

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 October 2003 (09.10.2003)

PCT

(10) International Publication Number
WO 03/082817 A2

(51) International Patent Classification⁷: C07D 211/36, (74) Common Representative: MERCK & CO., INC.; 126 A61K 31/495 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(21) International Application Number: PCT/US03/08723

(22) International Filing Date: 21 March 2003 (21.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/367,410 25 March 2002 (25.03.2002) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 03/082817 A2

(54) Title: BETA-AMINO HETEROCYCLIC DIPEPTIDYL PEPTIDASE INHIBITORS FOR THE TREATMENT OR PREVENTION OF DIABETES

(57) Abstract: The present invention is directed to compounds which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

TITLE OF THE INVENTION

BETA-AMINO HETEROCYCLIC DIPEPTIDYL PEPTIDASE INHIBITORS FOR
THE TREATMENT OR PREVENTION OF DIABETES

5 BACKGROUND OF THE INVENTION

Diabetes refers to a disease process derived from multiple causative factors and characterized by elevated levels of plasma glucose or hyperglycemia in the fasting state or after administration of glucose during an oral glucose tolerance test. Persistent or uncontrolled hyperglycemia is associated with increased and premature 10 morbidity and mortality. Often abnormal glucose homeostasis is associated both directly and indirectly with alterations of the lipid, lipoprotein and apolipoprotein metabolism and other metabolic and hemodynamic disease. Therefore, patients with diabetes are at especially increased risk of macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, 15 hypertension, nephropathy, neuropathy, and retinopathy. Consequently, therapeutical control of glucose homeostasis, lipid metabolism and hypertension are critically important in the clinical management and treatment of diabetes mellitus.

There are two generally recognized forms of diabetes. In type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), patients produce little or no 20 insulin, the hormone which regulates glucose utilization. In type 2 diabetes, or noninsulin dependent diabetes mellitus (NIDDM), patients often have plasma insulin levels that are the same or even elevated compared to nondiabetic subjects; however, these patients have developed a resistance to the insulin stimulating effect on glucose and lipid metabolism in the main insulin-sensitive tissues, which are muscle, liver and 25 adipose tissues, and the plasma insulin levels, while elevated, are insufficient to overcome the pronounced insulin resistance.

Insulin resistance is not primarily due to a diminished number of insulin receptors but to a post-insulin receptor binding defect that is not yet understood. This resistance to insulin responsiveness results in insufficient insulin 30 activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in the liver.

The available treatments for type 2 diabetes, which have not changed substantially in many years, have recognized limitations. While physical exercise and 35 reductions in dietary intake of calories will dramatically improve the diabetic

condition, compliance with this treatment is very poor because of well-entrenched sedentary lifestyles and excess food consumption, especially of foods containing high amounts of saturated fat. Increasing the plasma level of insulin by administration of sulfonylureas (e.g. tolbutamide and glipizide) or meglitinide, which stimulate the

5 pancreatic β -cells to secrete more insulin, and/or by injection of insulin when sulfonylureas or meglitinide become ineffective, can result in insulin concentrations high enough to stimulate the very insulin-resistant tissues. However, dangerously low levels of plasma glucose can result from administration of insulin or insulin secretagogues (sulfonylureas or meglitinide), and an increased level of insulin
10 resistance due to the even higher plasma insulin levels can occur. The biguanides increase insulin sensitivity resulting in some correction of hyperglycemia. However, the two biguanides, phenformin and metformin, can induce lactic acidosis and nausea/diarrhea. Metformin has fewer side effects than phenformin and is often prescribed for the treatment of type 2 diabetes.

15 The glitazones (i.e. 5-benzylthiazolidine-2,4-diones) are a more recently described class of compounds with potential for ameliorating many symptoms of type 2 diabetes. These agents substantially increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of type 2 diabetes resulting in partial or complete correction of the elevated plasma levels of glucose without
20 occurrence of hypoglycemia. The glitazones that are currently marketed are agonists of the peroxisome proliferator activated receptor (PPAR), primarily the PPAR-gamma subtype. PPAR-gamma agonism is generally believed to be responsible for the improved insulin sensitization that is observed with the glitazones. Newer PPAR agonists that are being tested for treatment of type 2 diabetes are agonists of the alpha,
25 gamma or delta subtype, or a combination of these, and in many cases are chemically different from the glitazones (i.e., they are not thiazolidinediones). Serious side effects (e.g. liver toxicity) have occurred with some of the glitazones, such as troglitazone.

Additional methods of treating diabetes are still under investigation.
30 New biochemical approaches that have been recently introduced or are still under development include treatment with alpha-glucosidase inhibitors (e.g. acarbose) and protein tyrosine phosphatase-1B (PTP-1B) inhibitors.

35 Compounds that are inhibitors of the dipeptidyl peptidase-IV ("DP-IV" or "DPP-IV") enzyme are also under investigation as drugs that may be useful in the treatment of diabetes, and particularly type 2 diabetes (See, for example, WO

97/40832, WO 98/19998, U.S. Patent No. 5,939,560, *Bioorg. Med. Chem. Lett.*, 6(10), 1163-1166 (1996); and *Bioorg. Med. Chem. Lett.*, 6(22), 2745-2748 (1996). The usefulness of DP-IV inhibitors in the treatment of type 2 diabetes is based on the fact that DP-IV *in vivo* readily inactivates glucagon like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). GLP-1 and GIP are incretins and are produced when food is consumed. The incretins stimulate production of insulin. Inhibition of DP-IV leads to decreased inactivation of the incretins, and this in turn results in increased effectiveness of the incretins in stimulating production of insulin by the pancreas. DP-IV inhibition therefore results in an increased level of serum insulin.

5 10 Advantageously, since the incretins are produced by the body only when food is consumed, DP-IV inhibition is not expected to increase the level of insulin at inappropriate times, such as between meals, which can lead to excessively low blood sugar (hypoglycemia). Inhibition of DP-IV is therefore expected to increase insulin without increasing the risk of hypoglycemia, which is a dangerous side effect

15 20 15 associated with the use of insulin secretagogues.

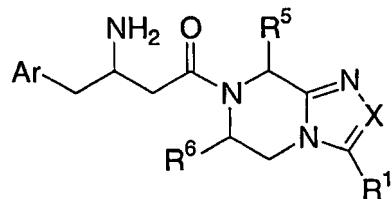
DP-IV inhibitors also have other therapeutic utilities, as discussed herein. DP-IV inhibitors have not been studied extensively to date, especially for utilities other than diabetes. New compounds are needed so that improved DP-IV inhibitors can be found for the treatment of diabetes and potentially other diseases and conditions.

SUMMARY OF THE INVENTION

The present invention is directed to compounds which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of the formula I:



I

5 wherein:

Ar is phenyl which is unsubstituted or substituted with 1-5 of R³, wherein R³ is independently selected from the group consisting of:

- (1) halogen,
- (2) C₁-6 alkyl, which is linear or branched and is unsubstituted or substituted with 1-5 halogens,
- (3) C₁-6 alkoxy, which is linear or branched and is unsubstituted or substituted with 1-5 halogens,
- (4) CN, and
- (5) hydroxy;

15

X is selected from the group consisting of:

- (1) N and
- (2) CR²;

20 R¹ and R² are each independently selected from the group consisting of:

- (1) hydrogen,
- (2) CN,
- (3) C₁-10 alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 halogens or phenyl, which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, CN, OH, R⁴, OR⁴, NHSO₂R⁴, SO₂R⁴, CO₂H, and CO₂C₁-6 alkyl, wherein the CO₂C₁-6 alkyl is linear or branched,
- (4) phenyl which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, CN, OH, R⁴, OR⁴, NHSO₂R⁴,

SO₂R⁴, CO₂H, and CO₂C₁₋₆alkyl, wherein the CO₂C₁₋₆ alkyl is linear or branched, and

(5) a 5- or 6-membered heterocycle which may be saturated or unsaturated comprising 1-4 heteroatoms independently selected from N, S and O, the heterocycle being unsubstituted or substituted with 1-3 substituents independently selected from oxo, OH, halogen, C₁₋₆alkyl, and OC₁₋₆alkyl, wherein C₁₋₆ alkyl and C₁₋₆ alkoxy are linear or branched and optionally substituted with 1-5 halogens;

10 R⁴ is C₁₋₆ alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 groups independently selected from halogen, CO₂H, and CO₂C₁₋₆ alkyl, wherein the CO₂C₁₋₆ alkyl is linear or branched;

R⁵ and R⁶ are each independently selected from the group consisting of:

15 (1) hydrogen,

(2) C₁₋₁₀ alkyl, which is linear or branched and which is unsubstituted or substituted with one or more substituents selected from:

(a) halogen,

(b) hydroxy,

20 (c) phenyl, wherein the phenyl is optionally substituted with 1-5 substituents independently selected from halogen, OH, C₁₋₆alkyl, and C₁₋₆ alkoxy, wherein the C₁₋₆ alkyl and C₁₋₆ alkoxy are linear or branched and optionally substituted with 1-5 halogens,

25 (d) naphthyl, wherein the naphthyl is optionally substituted with 1-5 substituents independently selected from halogen, OH, C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein the C₁₋₆ alkyl and C₁₋₆ alkoxy are linear or branched and optionally substituted with 1-5 halogens,

30 (e) CO₂H,

(f) CO₂C₁₋₆ alkyl,

(g) CONR⁷R⁸, wherein R⁷ and R⁸ are independently selected from the group consisting of hydrogen, tetrazolyl, phenyl,

C₃-6 cycloalkyl and C₁-6 alkyl, wherein C₁-6 alkyl is linear or branched and is optionally substituted with 1-6 substituents independently selected from 0-5 halogen and 0-1 phenyl, wherein the phenyl or C₃-6cycloalkyl being R⁷ or R⁸ or the optional phenyl substituent on the C₁-6alkyl are optionally substituted with 1-5 substituents independently selected from halogen, OH, C₁-6alkyl, and OC₁-6alkyl, said C₁-6alkyl and OC₁-6alkyl being linear or branched and optionally substituted with 1-5 halogens,

or wherein R⁷ and R⁸ are optionally joined to form a ring selected from pyrrolidine, piperidine or morpholine,

(3) CN,

(4) phenyl which is unsubstituted or substituted with 1-5 substituents independently selected from C₁-6 alkyl, C₁-6 alkoxy, hydroxy and halogen, wherein the C₁-6 alkyl and C₁-6 alkoxy are linear or branched and optionally substituted with 1-5 halogens,

(5) naphthyl which is unsubstituted or substituted with 1-5 substituents independently selected from C₁-6 alkyl, C₁-6 alkoxy, hydroxy and halogen, wherein the C₁-6 alkyl and C₁-6 alkoxy are linear or branched and optionally substituted with 1-5 halogens,

(6) CO₂H,

(7) CO₂C₁-6 alkyl,

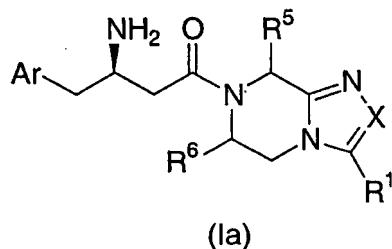
(8) CONR⁷R⁸, and

(9) C₃-6 cycloalkyl, which is optionally substituted with 1-5 substituents independently selected from halogen, OH, C₁-6 alkyl, and C₁-6 alkoxy, wherein the C₁-6 alkyl and C₁-6 alkoxy are linear or branched and optionally substituted with 1-5 halogens,

with the proviso that one of R⁵ and R⁶ is other than hydrogen;

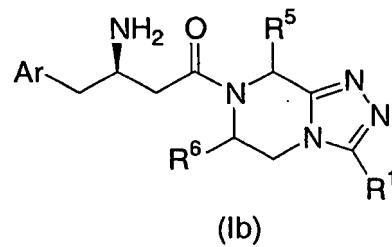
or a pharmaceutically acceptable salt thereof or an individual diastereomer thereof.

An embodiment of the present invention includes compounds of the formula Ia:



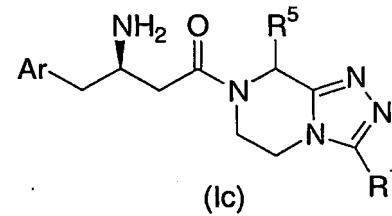
wherein X, Ar, R¹, R⁵ and R⁶ are defined herein;
or a pharmaceutically acceptable salt or an individual diastereomer thereof.

Another embodiment of the present invention includes compounds of
5 the formula Ib:



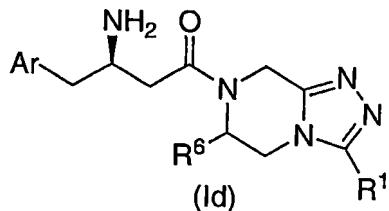
wherein Ar, R¹, R⁵ and R⁶ are defined herein;
or a pharmaceutically acceptable salt or an individual diastereomer thereof.

Another embodiment of the present invention includes compounds of
10 the formula Ic:



wherein Ar, R¹ and R⁵ are defined herein;
or a pharmaceutically acceptable salt thereof or an individual diastereomer thereof.

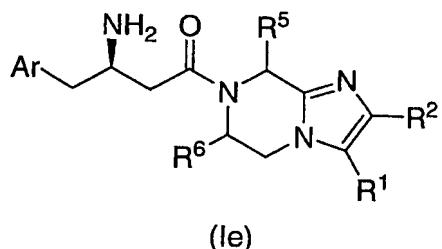
Another embodiment of the present invention includes compounds of
15 the formula Id:



wherein Ar, R¹ and R⁶ are defined herein;

or a pharmaceutically acceptable salt thereof or an individual diastereomer thereof.

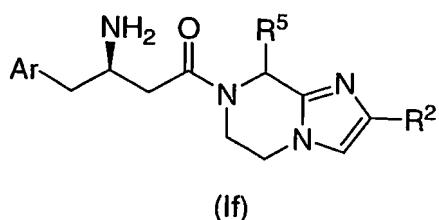
Another embodiment of the present invention includes compounds of
5 the formula Ie:



wherein Ar, R¹, R², R⁵ and R⁶ are defined herein;

or a pharmaceutically acceptable salt or an individual diastereomer thereof.

Another embodiment of the present invention includes compounds of
10 the formula If:



wherein Ar, R² and R⁵ are defined herein;

and pharmaceutically acceptable salts and individual diastereomers thereof.

15 In the present invention it is preferred that Ar is phenyl which is unsubstituted or substituted with 1-5 substituents which are independently selected from the group consisting of:

- (1) fluoro,
- (2) chloro, and

(3) CF_3 .

In the present invention it is more preferred that Ar is selected from the group consisting of:

5 (1) phenyl,
(2) 2-fluorophenyl,
(3) 3,4-difluorophenyl,
(4) 2,5-difluorophenyl,
(5) 2,4,5-trifluorophenyl, and
10 (6) 2-fluoro-4-(trifluoromethyl)phenyl.

In the present invention it is preferred that R^1 is selected from the group consisting of:

15 (1) hydrogen and
(2) C_{1-6} alkyl, which is linear or branched and which is unsubstituted or substituted with phenyl or 1-5 fluorines.

In the present invention it is more preferred that R^1 is selected from the group consisting of:

20 (1) hydrogen,
(2) methyl,
(3) ethyl,
(4) CF_3 ,
(5) CH_2CF_3 ,
25 (6) CF_2CF_3 , and
(7) benzyl.

In the present invention it is more preferred that R^1 is selected from the group consisting of:

30 (1) hydrogen,
(2) methyl,
(3) ethyl,
(4) CF_3 , and
(5) CH_2CF_3 .

In the present invention it is even more preferred that R¹ is hydrogen or CF₃.

5 In the present invention it is preferred that R² is selected from:

- (1) hydrogen,
- (2) C₁-6alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 fluorines, and
- (3) phenyl, which is unsubstituted or substituted with 1-3 substituents independently selected from fluoro, OCH₃, and OCF₃.

10

In the present invention it is more preferred that R² is selected from the group consisting of:

- 15 (1) hydrogen,
- (2) methyl,
- (3) ethyl,
- (4) CF₃,
- (5) CH₂CF₃,
- 20 (6) CF₂CF₃,
- (7) phenyl,
- (8) (4-methoxy)phenyl,
- (9) (4-trifluoromethoxy)phenyl,
- (10) 4-fluorophenyl, and
- 25 (11) 3,4-difluorophenyl.

In the present invention it is even more preferred that R² is CF₃ or CF₂CF₃.

30 In the present invention it is preferred that R⁵ and R⁶ are independently selected from the group consisting of:

- (1) hydrogen,
- (2) C₁-10 alkyl, which is linear or branched and which is unsubstituted or substituted with one or more substituents selected from:

(a) halogen,
(b) hydroxy,
(c) phenyl, wherein the phenyl is optionally substituted with 1-5
substituents independently selected from halogen, OH,
C₁₋₆ alkyl, and C₁₋₆ alkoxy, wherein the C₁₋₆ alkyl and C₁₋₆
alkoxy are linear or branched and optionally substituted with 1-
5 halogens,
(d) CO₂H,
(e) CO₂C₁₋₆ alkyl,
10 (f) CONR⁷R⁸, wherein R⁷ and R⁸ are independently selected
from the group consisting of hydrogen, tetrazolyl, phenyl,
C₃₋₆ cycloalkyl and C₁₋₆ alkyl, wherein C₁₋₆ alkyl is linear or
branched and is optionally substituted with 1-6 substituents
independently selected from 0-5 halogen and 0-1 phenyl,
15 wherein the phenyl or C₃₋₆ cycloalkyl being R⁷ or the optional
phenyl substituent on the C₁₋₆ alkyl are optionally substituted
with 1-5 substituents independently selected from halogen, OH,
C₁₋₆ alkyl, and C₁₋₆ alkoxy, said C₁₋₆ alkyl and C₁₋₆ alkoxy
being linear or branched and optionally substituted with 1-5
halogens,
20 or wherein R⁷ and R⁸ are optionally joined to form a ring
selected from pyrrolidine, piperidine or morpholine,
(3) CN,
(4) phenyl which is unsubstituted or substituted with 1-5 substituents
25 independently selected from C₁₋₆alkyl, OC₁₋₆alkyl, hydroxy and
halogen, wherein the C₁₋₆alkyl and OC₁₋₆alkyl are linear or branched
and optionally substituted with 1-5 halogen,
(5) CO₂H,
(6) CO₂C₁₋₆alkyl,
30 (7) CONR⁷R⁸, and
(8) C₃₋₆ cycloalkyl, which is optionally substituted with 1-5 substituents
independently selected from halogen, OH, C₁₋₆ alkyl, and C₁₋₆
alkoxy, wherein the C₁₋₆ alkyl and C₁₋₆ alkoxy are linear or branched
and optionally substituted with 1-5 halogens,
35 with the proviso that one of R⁵ and R⁶ is other than hydrogen.

In the present invention it is more preferred that R⁵ and R⁶ are independently selected from the group consisting of:

5 (1) hydrogen,
(2) C₁-10 alkyl, which is linear or branched and which is unsubstituted or substituted with one or more substituents selected from:
(a) halogen,
(b) phenyl, wherein the phenyl is optionally substituted with 1-5 substituents independently selected from halogen, OH,
10 C₁-6 alkyl, and C₁-6 alkoxy, wherein the C₁-6 alkyl and C₁-6 alkoxy are linear or branched and optionally substituted with 1-5 halogens,
(3) phenyl which is unsubstituted or substituted with 1-3 substituents independently selected from C₁-6alkyl, OC₁-6alkyl, and halogen, wherein the C₁-6alkyl and OC₁-6alkyl are linear or branched and optionally substituted with 1-5 halogens, and
15 (4) CO₂C₁-6 alkyl,
with the proviso that one of R⁵ and R⁶ is other than hydrogen.

20 In the present invention it is more preferred that R⁵ and R⁶ are independently selected from the group consisting of:

25 (1) hydrogen,
(2) CH₃,
(3) CH₂CH₃,
(4) CH(CH₃)₂,
(5) COOCH₃,
(6) CH₂-phenyl,
(7) 3-fluorophenyl, and
30 (8) 2-(trifluoromethyl)phenyl,
with the proviso that one of R⁵ and R⁶ is other than hydrogen.

In the present invention it is even more preferred that R⁵ and R⁶ are independently hydrogen or CH₃, with the proviso that one of R⁵ and R⁶ is other than hydrogen.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The compounds of the instant invention have one asymmetric center at the beta carbon atom.

5 Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is
10 meant to comprehend all such isomeric forms of these compounds.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

15 Some of the compounds described herein may exist as tautomers, which have different points of attachment of hydrogen accompanied by one or more double bond shifts. For example, a ketone and its enol form are keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of the present invention.

20 Formula I shows the structure of the class of compounds without preferred stereochemistry. Formula Ia shows the preferred stereochemistry at the carbon atom that is attached to the amine group of the beta amino acid from which these compounds are prepared.

25 The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

30 If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the
35 formation of salts using an enantiomerically pure acid or base. The diastereomeric

derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

5 Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or 10 organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the 15 form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, 20 ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be 25 prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the 30 like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

As appreciated by those of skill in the art, halo or halogen as used 35 herein are intended to include fluoro, chloro, bromo and iodo. Similarly, C1-6, as in

C₁-6 alkyl is defined to identify the group as having 1, 2, 3, 4, 5, or 6 carbons in a linear or branched arrangement, such that C₁-6 alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and hexyl. Likewise, C₀, as in C₀alkyl is defined to identify the presence of a direct covalent bond. A

5 group which is designated as being independently substituted with substituents may be independently substituted with multiple numbers of such substituents. The term "heterocycle" as used herein is intended to include 5- or 6-membered ring systems which are within the following listing: benzimidazolyl, benzodioxanyl, benzofuranyl, benzopyrazolyl, benzothiadiazolyl, benzotriazolyl, benzothiophenyl, benzoxadiazolyl,

10 benzoxazolyl, carbazolyl, carbolinyl, chromanyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrazolyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, triazolyl,

15 azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl,

20 dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, tetrahydroimidazolyl, tetrahydroisoquinolinyl, and tetrahydrothienyl.

Exemplifying the invention is the use of the compounds disclosed in
25 the Examples and herein.

Specific compounds within the present invention include a compound which is selected from the group consisting of the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

30 The subject compounds are useful in a method of inhibiting the dipeptidyl peptidase-IV enzyme in a patient such as a mammal in need of such inhibition comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as inhibitors of dipeptidyl peptidase-IV enzyme activity.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

The present invention is further directed to a method for the manufacture of a medicament for inhibiting dipeptidyl peptidase-IV enzyme activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The subject treated in the present methods is generally a mammal, preferably a human being, male or female, in whom inhibition of dipeptidyl peptidase-IV enzyme activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. As used herein, the term "treatment" refers both to the treatment and to the prevention or prophylactic therapy of the mentioned conditions.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and/or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The utility of the compounds in accordance with the present invention as inhibitors of dipeptidyl peptidase-IV enzyme activity may be demonstrated by methodology known in the art. Inhibition constants are determined as follows. A continuous fluorometric assay is employed with the substrate Gly-Pro-AMC, which is

5 cleaved by DP-IV to release the fluorescent AMC leaving group. The kinetic parameters that describe this reaction are as follows: $K_m = 50 \mu\text{M}$; $k_{cat} = 75 \text{ s}^{-1}$; $k_{cat}/K_m = 1.5 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$. A typical reaction contains approximately 50 pM enzyme, 50 μM Gly-Pro-AMC, and buffer (100 mM HEPES, pH 7.5, 0.1 mg/ml BSA) in a total reaction volume of 100 μL . Liberation of AMC is monitored continuously in a

10 96-well plate fluorometer using an excitation wavelength of 360 nm and an emission wavelength of 460 nm. Under these conditions, approximately 0.8 μM AMC is produced in 30 minutes at 25 degrees C. The enzyme used in these studies was soluble (transmembrane domain and cytoplasmic extension excluded) human protein produced in a baculovirus expression system (Bac-To-Bac, Gibco BRL). The kinetic

15 constants for hydrolysis of Gly-Pro-AMC and GLP-1 were found to be in accord with literature values for the native enzyme. To measure the dissociation constants for compounds, solutions of inhibitor in DMSO were added to reactions containing enzyme and substrate (final DMSO concentration is 1%). All experiments were conducted at room temperature using the standard reaction conditions described

20 above. To determine the dissociation constants (K_i), reaction rates were fit by non-linear regression to the Michaelis-Menton equation for competitive inhibition. The errors in reproducing the dissociation constants are typically less than two-fold.

In particular, the compounds of the following examples had activity in inhibiting the dipeptidyl peptidase-IV enzyme in the aforementioned assays, generally with an IC₅₀ of less than about 1 μM . Such a result is indicative of the intrinsic activity of the compounds in use as inhibitors the dipeptidyl peptidase-IV enzyme activity.

Dipeptidyl peptidase-IV enzyme (DP-IV) is a cell surface protein that has been implicated in a wide range of biological functions. It has a broad tissue distribution (intestine, kidney, liver, pancreas, placenta, thymus, spleen, epithelial cells, vascular endothelium, lymphoid and myeloid cells, serum), and distinct tissue and cell-type expression levels. DP-IV is identical to the T cell activation marker CD26, and it can cleave a number of immunoregulatory, endocrine, and neurological peptides *in vitro*. This has suggested a potential role for this peptidase in a variety of disease processes in humans or other species.

The compounds of the present invention have utility in treating, preventing, ameliorating, controlling or reducing the risk of one or more of the following conditions or diseases: (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, 5 (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) 10 nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), (25) type 2 diabetes, (26) growth hormone deficiency, (27) neutropenia, (28) neuronal disorders, (29) tumor metastasis, (30) benign prostatic hypertrophy, (32) gingivitis, (33) hypertension, (34) osteoporosis, and other 15 conditions that may be treated or prevented by inhibition of DP-IV.

15 The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein.

Type 2 Diabetes and Related Disorders: It is well established that the incretins GLP-1 20 and GIP are rapidly inactivated *in vivo* by DP-IV. Studies with DP-IV^(-/-)-deficient mice and preliminary clinical trials indicate that DP-IV inhibition increases the steady state concentrations of GLP-1 and GIP, resulting in improved glucose tolerance. By analogy to GLP-1 and GIP, it is likely that other glucagon family peptides involved in glucose regulation are also inactivated by DP-IV (e.g. PACAP). Inactivation of these 25 peptides by DP-IV may also play a role in glucose homeostasis. The DP-IV inhibitors of the present invention therefore have utility in the treatment, prevention, amelioration, control or reduction of the risk of Type 2 diabetes and in the treatment, prevention, amelioration, control or reduction of the risk of the numerous conditions that often accompany Type 2 diabetes, including metabolic syndrome X, reactive 30 hypoglycemia, and diabetic dyslipidemia. Obesity, discussed below, is another condition that is often found with Type 2 diabetes that may respond to treatment with the compounds of this invention.

The following diseases, disorders and conditions are related to Type 2 diabetes, and therefore may be treated, controlled, ameliorated or prevented, by 35 administering the compounds of this invention: (1) hyperglycemia, (2) low glucose

tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, 5 including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component.

10

Obesity: DP-IV inhibitors may be useful for the treatment of obesity. This is based on the observed inhibitory effects on food intake and gastric emptying of GLP-1 and GLP-2. Exogenous administration of GLP-1 in humans significantly decreases food intake and slows gastric emptying (Am. J. Physiol. 277, R910-R916 (1999)). ICV 15 administration of GLP-1 in rats and mice also has profound effects on food intake (Nature Medicine 2, 1254-1258 (1996)). This inhibition of feeding is not observed in GLP-1R^(-/-) mice, indicating that these effects are mediated through brain GLP-1 receptors. By analogy to GLP-1, it is likely that GLP-2 is also regulated by DP-IV. ICV administration of GLP-2 also inhibits food intake, analogous to the effects 20 observed with GLP-1 (Nature Medicine 6, 802-807 (2000)). In addition, studies with DP-IV deficient mice suggest that these animals are resistant to diet-induced obesity and associated pathology (e.g. hyperinsulinemia).

Growth Hormone Deficiency: DP-IV inhibition may be useful for the treatment of 25 growth hormone deficiency, based on the hypothesis that growth-hormone releasing factor (GRF), a peptide that stimulates release of growth hormone from the anterior pituitary, is cleaved by the DP-IV enzyme *in vivo* (WO 00/56297). The following data provide evidence that GRF is an endogenous substrate: (1) GRF is efficiently cleaved *in vitro* to generate the inactive product GRF[3-44] (BBA 1122, 147-153 30 (1992)); (2) GRF is rapidly degraded in plasma to GRF[3-44]; this is prevented by the DP-IV inhibitor diprotin A; and (3) GRF[3-44] is found in the plasma of a human GRF transgenic pig (J. Clin. Invest. 83, 1533-1540 (1989)). Thus DP-IV inhibitors may be useful for the same spectrum of indications which have been considered for growth hormone secretagogues.

35

Intestinal Injury: The potential for using DP-IV inhibitors for the treatment of intestinal injury is suggested by the results of studies indicating that glucagon-like peptide-2 (GLP-2), a likely endogenous substrate for DP-IV, may exhibit trophic effects on the intestinal epithelium (Regulatory Peptides 90, 27-32 (2000)).

5 Administration of GLP-2 results in increased small bowel mass in rodents and attenuates intestinal injury in rodent models of colitis and enteritis.

Immunosuppression: DP-IV inhibition may be useful for modulation of the immune response, based upon studies implicating the DP-IV enzyme in T cell activation and in

10 chemokine processing, and efficacy of DP-IV inhibitors in *in vivo* models of disease. DP-IV has been shown to be identical to CD26, a cell surface marker for activated immune cells. The expression of CD26 is regulated by the differentiation and activation status of immune cells. It is generally accepted that CD26 functions as a co-stimulatory molecule in *in vitro* models of T cell activation. A number of
15 chemokines contain proline in the penultimate position, presumably to protect them from degradation by non-specific aminopeptidases. Many of these have been shown to be processed *in vitro* by DP-IV. In several cases (RANTES, LD78-beta, MDC, eotaxin, SDF-1alpha), cleavage results in an altered activity in chemotaxis and signaling assays. Receptor selectivity also appears to be modified in some cases
20 (RANTES). Multiple N-terminally truncated forms of a number of chemokines have been identified in *in vitro* cell culture systems, including the predicted products of DP-IV hydrolysis.

DP-IV inhibitors have been shown to be efficacious immunosuppressants in animal models of transplantation and arthritis. Prodipine (Pro-
25 Pro-diphenyl-phosphonate), an irreversible inhibitor of DP-IV, was shown to double cardiac allograft survival in rats from day 7 to day 14 (Transplantation 63, 1495-1500 (1997)). DP-IV inhibitors have been tested in collagen and alkyldiamine-induced arthritis in rats and showed a statistically significant attenuation of hind paw swelling in this model (Int. J. Immunopharmacology 19, 15-24 (1997), Immunopharmacology
30 40, 21-26 (1998)). DP-IV is upregulated in a number of autoimmune diseases including rheumatoid arthritis, multiple sclerosis, Graves' disease, and Hashimoto's thyroiditis (Immunology Today 20, 367-375 (1999)).

HIV Infection: DP-IV inhibition may be useful for the treatment or prevention of HIV
35 infection or AIDS because a number of chemokines which inhibit HIV cell entry are

potential substrates for DP-IV (Immunology Today 20, 367-375 (1999)). In the case of SDF-1alpha, cleavage decreases antiviral activity (PNAS 95, 6331-6 (1998)). Thus, stabilization of SDF-1alpha through inhibition of DP-IV would be expected to decrease HIV infectivity.

5

Hematopoiesis: DP-IV inhibition may be useful for the treatment or prevention of hematopoiesis because DP-IV may be involved in hematopoiesis. A DP-IV inhibitor, Val-Boro-Pro, stimulated hematopoiesis in a mouse model of cyclophosphamide-induced neutropenia (WO 99/56753).

10

Neuronal Disorders: DP-IV inhibition may be useful for the treatment or prevention of various neuronal or psychiatric disorders because a number of peptides implicated in a variety of neuronal processes are cleaved *in vitro* by DP-IV. A DP-IV inhibitor thus may have a therapeutic benefit in the treatment of neuronal disorders.

15

Endomorphin-2, beta-casomorphin, and substance P have all been shown to be *in vitro* substrates for DP-IV. In all cases, *in vitro* cleavage is highly efficient, with $k_{cat}/K_m \sim 10^6 M^{-1}s^{-1}$ or greater. In an electric shock jump test model of analgesia in rats, a DP-IV inhibitor showed a significant effect that was independent of the presence of exogenous endomorphin-2 (Brain Research 815, 278-286 (1999)).

20

Tumor Invasion and Metastasis: DP-IV inhibition may be useful for the treatment or prevention of tumor invasion and metastasis because an increase or decrease in expression of several ectopeptidases including DP-IV has been observed during the transformation of normal cells to a malignant phenotype (J. Exp. Med. 190, 301-305

25

(1999)). Up- or down-regulation of these proteins appears to be tissue and cell-type specific. For example, increased CD26/DP-IV expression has been observed on T cell lymphoma, T cell acute lymphoblastic leukemia, cell-derived thyroid carcinomas, basal cell carcinomas, and breast carcinomas. Thus, DP-IV inhibitors may have utility in the treatment of such carcinomas.

30

Benign Prostatic Hypertrophy: DP-IV inhibition may be useful for the treatment of benign prostatic hypertrophy because increased DP-IV activity was noted in prostate tissue from patients with BPH (Eur. J. Clin. Chem. Clin. Biochem 30, 333-338 (1992)).

35

Sperm motility/male contraception: DP-IV inhibition may be useful for the altering sperm motility and for male contraception because in seminal fluid, prostatosomes, prostate derived organelles important for sperm motility, possess very high levels of DP-IV activity (Eur. J. Clin. Chem. Clin. Biochem 30, 333-338 (1992)).

5

Gingivitis: DP-IV inhibition may be useful for the treatment of gingivitis because DP-IV activity was found in gingival crevicular fluid and in some studies correlated with periodontal disease severity (Arch. Oral Biol. 37, 167-173 (1992)).

10 Osteoporosis: DP-IV inhibition may be useful for the treatment or prevention of osteoporosis because GIP receptors are present in osteoblasts.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the

15 aforementioned diseases, disorders and conditions in combination with other agents.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of Formula I or the other drugs may have utility, where the combination of the drugs together are safer or 20 more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula I is

25 preferred. However, the combination therapy may also include therapies in which the compound of Formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly.

30 Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I.

Examples of other active ingredients that may be administered in combination with a compound of Formula I, and either administered separately or in the same pharmaceutical composition, include, but are not limited to:

- (a) other dipeptidyl peptidase IV (DP-IV) inhibitors;
- 5 (b) insulin sensitizers including ligands for PPAR receptors (alpha and/or gamma and/or beta-delta) which have activity as agonists, antagonists, selective activators, or partial agonists, including (i) PPAR γ agonists such as the glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555, rosiglitazone, and the like) and other PPAR ligands, including PPAR α/γ dual agonists, such as KRP-297, PPAR α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), and PPAR γ partial agonists, (ii) biguanides such as metformin and phenformin, and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;
- 10 (c) insulin or insulin mimetics;
- 15 (d) sulfonylureas and other insulin secretagogues such as tolbutamide and glipizide, meglitinide, and related materials;
- (e) α -glucosidase inhibitors (such as acarbose);
- (f) glucagon receptor antagonists such as those disclosed in WO 98/04528, WO 99/01423, WO 00/39088, and WO 00/69810;
- 20 (g) GLP-1, GLP-1 mimetics, GLP-1 receptor agonists, and exendins such as those disclosed in WO00/42026 and WO00/59887;
- (h) GIP and GIP mimetics such as those disclosed in WO00/58360, and GIP receptor agonists;
- (i) PACAP, PACAP mimetics, and PACAP receptor agonists such as
- 25 those disclosed in WO 01/23420;
- (j) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, rosuvastatin, and other statins), (ii) sequestrants (cholestyramine, colestipol, and dialkylaminoalkyl derivatives of a cross-linked dextran), (iii) nicotinyl
- 30 alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and bezafibrate), (v) PPAR α/γ dual agonists, such as KRP-297, (vi) inhibitors of cholesterol absorption, such as beta-sitosterol and ezetimibe, (vii) acyl CoA:cholesterol acyltransferase inhibitors, such as avasimibe, and (viii) anti-oxidants, such as probucol;
- 35 (k) PPAR δ agonists, such as those disclosed in WO97/28149;

(l) antiobesity compounds such as fenfluramine, dexfenfluramine, phentermine, sibutramine, orlistat, neuropeptide Y5 receptor antagonists, melanocortin 4 receptor agonists, cannabinoid CB-1 receptor antagonists such as rimonabant, and β 3 adrenergic receptor agonists;

5 (m) ileal bile acid transporter inhibitors;

(n) antihypertensives including those acting on the angiotensin or renin systems, such as angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists or renin inhibitors, such as captopril, cilazapril, enalapril, fosinopril, lisinopril, quinapril, ramipril, zofenopril, candesartan, cilexetil, eprosartan,

10 irbesartan, losartan, tasosartan, telmisartan, and valsartan; and

(o) agents intended for use in inflammatory conditions such as aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclooxygenase 2 selective inhibitors.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds. Non-limiting examples include combinations of compounds having Formula I with two or more active compounds selected from biguanides, sulfonylureas, HMG-CoA reductase inhibitors, PPAR agonists, PTP-1B inhibitors, other DP-IV inhibitors, and anti-obesity compounds.

20 Likewise, compounds of the present invention may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

25 The weight ratio of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range

from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200.

Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

5 In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

10 The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for 15 each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

20 The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier 25 or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which 30 results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

35 The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to

any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the

5 active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and

10 lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glycetyl monostearate or glycetyl distearate may be employed. They may also be coated by the techniques

15 described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules

20 wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose,

25 hydroxy- propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example

30 heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives,

35 for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one

or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

10 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

15 The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example 20 gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

25 Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

30 The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, 35 Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils

are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

5 The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

10 For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed (for purposes of this application, topical application shall include mouth washes and gargles).

15 The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

20 In the treatment, prevention, control, amelioration, or reduction of risk of conditions which require inhibition of dipeptidyl peptidase-IV enzyme activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets

25 containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

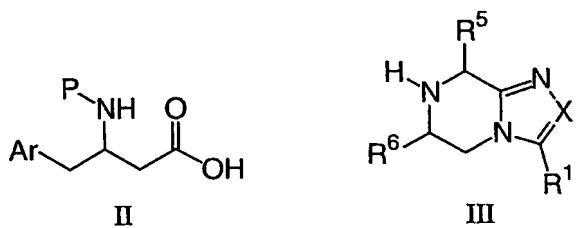
30 When treating, preventing, controlling, ameliorating, or reducing the risk of diabetes mellitus and/or hyperglycemia or hypertriglyceridemia or other diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per

kilogram of animal body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, preferably from about 1 milligrams to about 50 milligrams. In the case of a 70 kg 5 adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

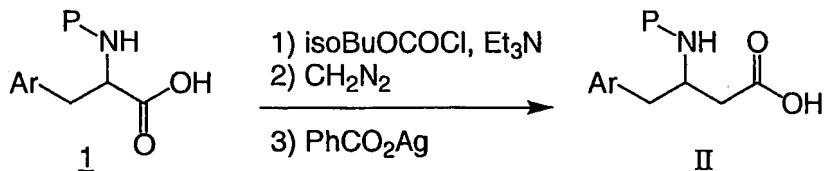
It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a 10 variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are 15 illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein.

The compounds of the present invention can be prepared from beta amino acid intermediates such as those of formula II and substituted heterocyclic intermediates such as those of formula III, using standard peptide coupling conditions 20 followed by deprotection. The preparation of these intermediates is described in the following schemes.

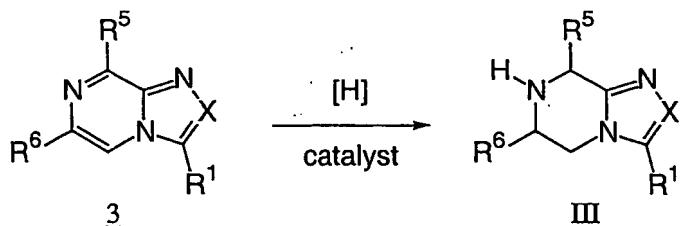


where Ar, X, R¹, R⁵ and R⁶ are as defined above and P is a suitable nitrogen protecting group such as tert-butoxycarbonyl, benzyloxycarbonyl, or 9-fluorenylmethoxy- 25 carbonyl.

SCHEME 1

Compounds of formula II are commercially available, known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One common route is illustrated in Scheme 1. Acid I, which may be commercially available or readily prepared from the corresponding amino acid by protection using, for example, di-*tert*-butyl-dicarbonate (for P = Boc), carbobenzyloxy chloride (for P = Cbz), or *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (for P = Fmoc), is treated with isobutyl chloroformate and a base such as triethylamine or diisopropylethylamine, followed by diazomethane. The resultant diazoketone is then treated with silver benzoate in a solvent such as methanol or aqueous dioxane and may be subjected to sonication following the procedure of Sewald et al., *Synthesis*, 837 (1997) in order to provide the beta amino acid II. As will be understood by those skilled in the art, for the preparation of enantiomerically pure beta amino acids II, enantiomerically pure alpha amino acids I may be used. Alternate routes to these compounds can be found in the following reviews: E. Juaristi, *Enantioselective Synthesis of β -Amino Acids*, Ed., Wiley-VCH, New York: 1997, Juaristi et al., *Aldrichimica Acta*, 27, 3 (1994), Cole et al., *Tetrahedron*, 32, 9517 (1994).

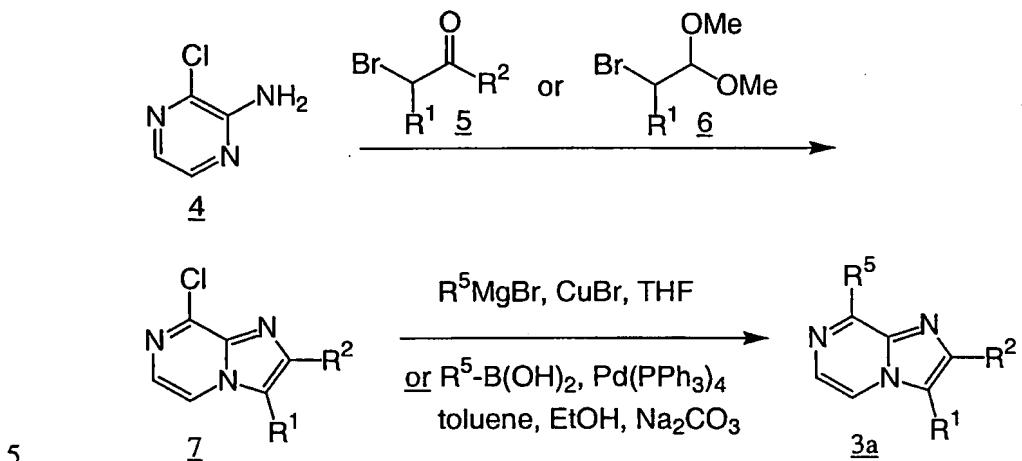
20

SCHEME 2

Compounds III are commercially available, known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One convenient method is shown in Scheme 2. Unsaturated derivative 3 is reduced, for example, by treatment with hydrogen gas and a catalyst such as palladium

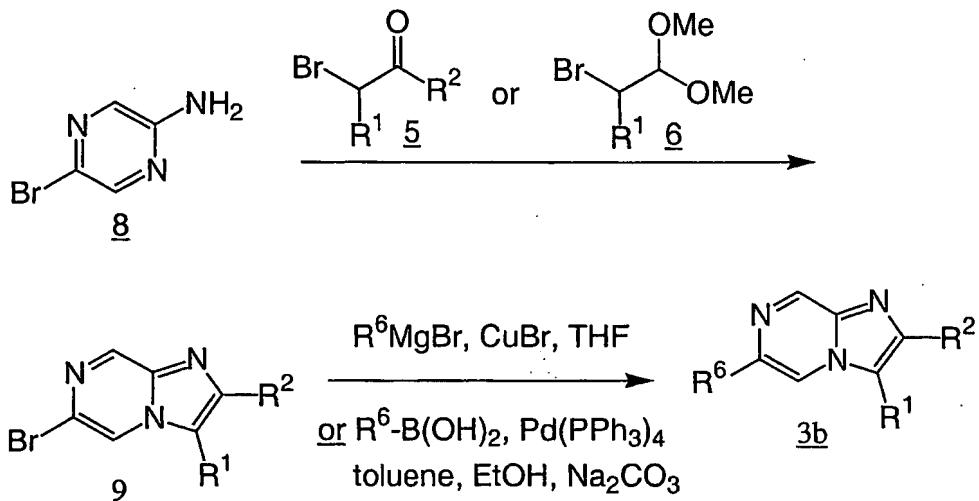
on carbon or platinum oxide in a solvent such as methanol or ethanol to provide Compound III.

SCHEME 3



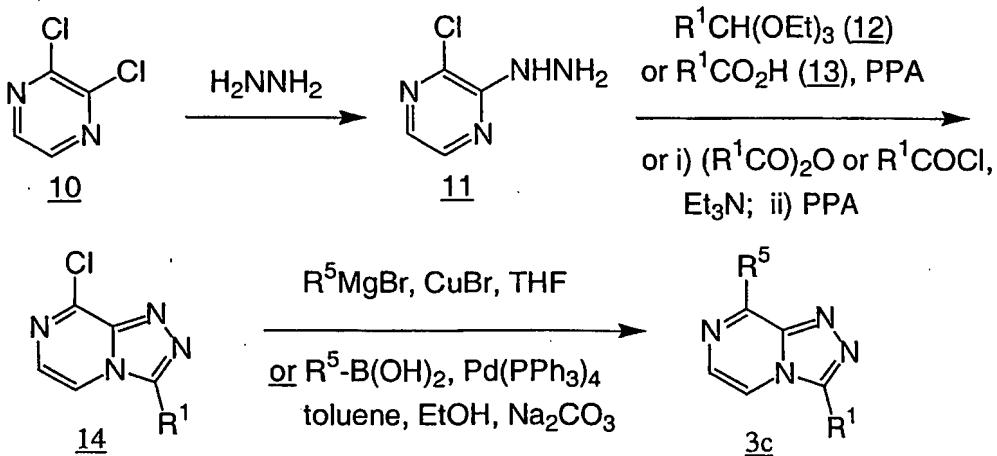
Intermediates 3, from Scheme 2, are themselves commercially available, known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art. One such method when X is CR² and R⁶ is H is illustrated in Scheme 3. Aminopyrazine 4 is treated with a 2-haloketone such as 2-bromoketone 5 in a solvent such as methanol or ethanol to provide intermediate 7. Alternatively, for the preparation of intermediate 7 where R² is H, 2-bromo-dimethylacetal 6 and a catalytic amount of acid such as hydrochloric acid may be employed instead of intermediate 5. The conversion of 4 to 7 may also be carried out in two steps. First, 4 and an appropriate bromide 5 are heated, conveniently in a solvent such as dioxane at 50 °C for 16 h. Then, solvent is removed, the residue treated with isopropanol, and the mixture heated at reflux for approximately 2 h. Intermediate 7 is converted to 3a by treatment with a Grignard reagent in the presence of copper bromide according to the literature procedure (*J. Org. Chem.* 1987, 52, 3847) or by palladium catalyzed Suzuki coupling of a boronic acid.

SCHEME 4



Intermediates 3b, wherein X is CR^2 and R^5 is H , may be prepared as described above for Scheme 3 starting with aminopyrazine 8, as illustrated in Scheme 5 4.

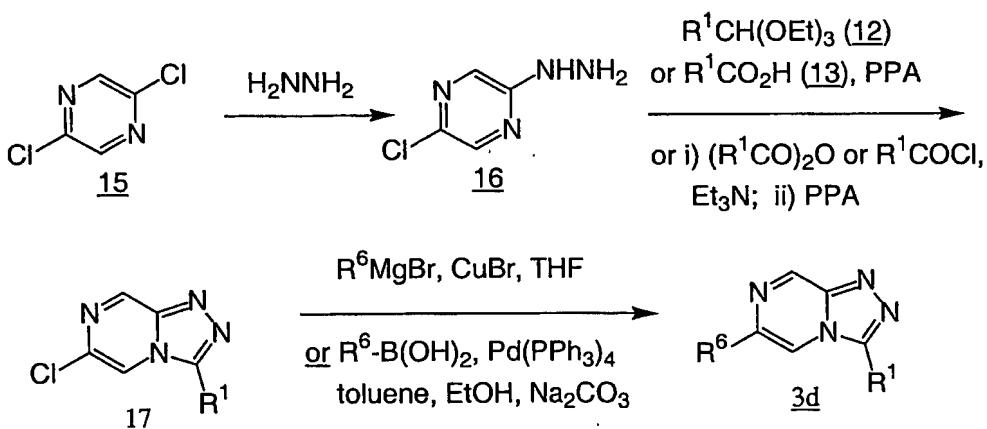
SCHEME 5



An alternate route for the preparation of Compound 3c wherein X is N and R^6 is H is illustrated in Scheme 5. Dichloropyrazine 10 is treated with hydrazine to provide hydrazinopyrazine 11. Compound 11 may be condensed with either an orthoester such as triethyl orthoester 12 or with a carboxylic acid 13 in

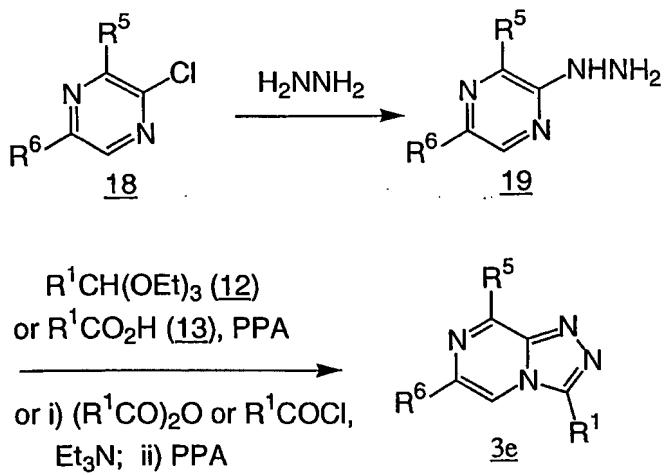
polyphosphoric acid at elevated temperatures to give 14. Alternatively, the hydrazine 11 may be acylated, for example, by treatment with an acid chloride or anhydride in the presence of a base such as triethylamine, and the resultant hydrazide cyclized to 14 by heating in polyphosphoric acid. Displacement of the halide using a Grignard reagent or Suzuki coupling as described above provides 3c.

SCHEME 6



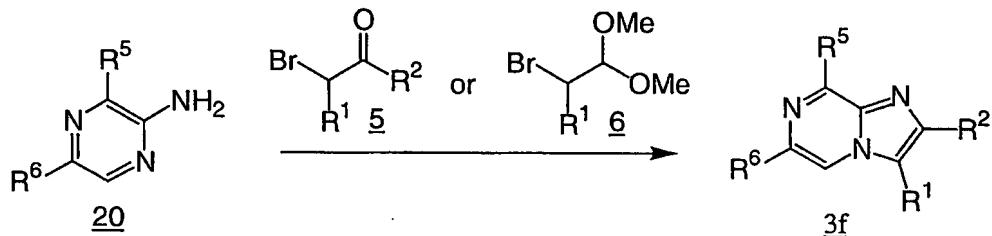
Intermediates 3d, wherein X is N and R⁵ is H, may be prepared as described above for Scheme 5 starting with dichloropyrazine 15, as illustrated in Scheme 6.

SCHEME 7



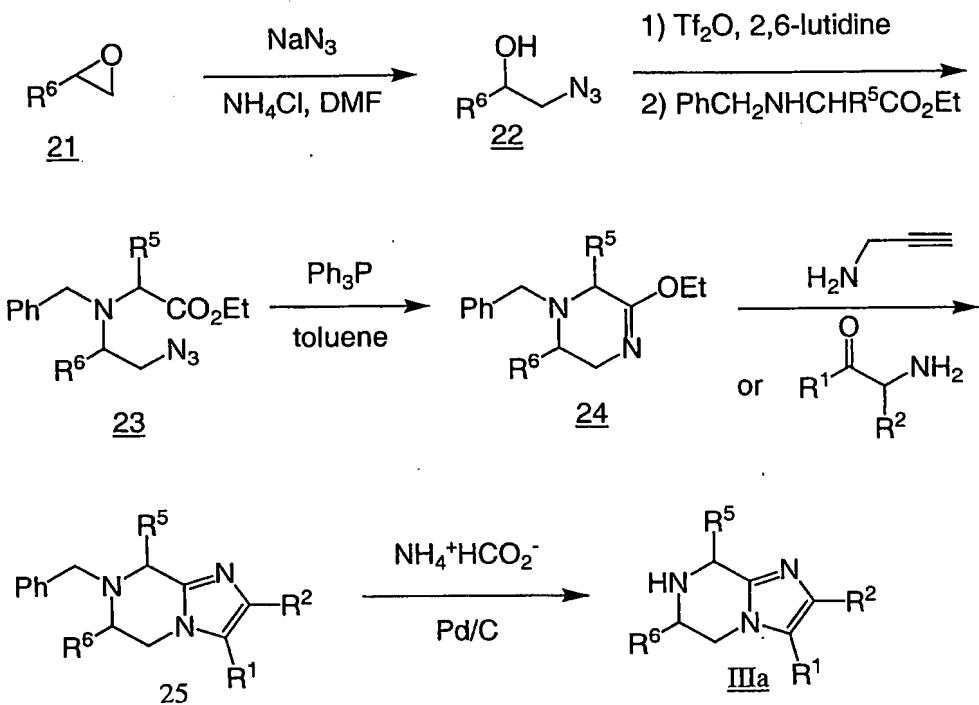
Intermediates 3e, wherein X is N, may be prepared from chloropyrazine 18 as illustrated in Scheme 7. Chloropyrazine 18, which is commercially available, known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art, is treated with hydrazine to provide hydrazinopyrazine 19. Intermediate 19 may be condensed with either an orthoester such as triethyl orthoester 12 or with a carboxylic acid 13 in polyphosphoric acid at elevated temperatures to give 3e. Alternatively, the hydrazine 19 may be acylated, for example, by treatment with an acid chloride or anhydride in the presence of a base such as triethylamine, and the resultant hydrazide cyclized to 3e by heating in polyphosphoric acid.

SCHEME 8



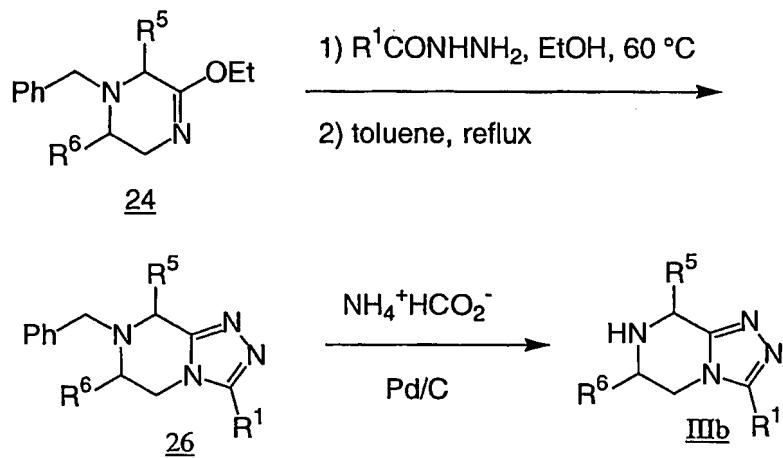
Intermediates 3f, wherein X is CR², may also be prepared as illustrated in Scheme 8. Aminopyrazine 20, which is commercially available, known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art, is treated with a 2-haloketone such as 2-bromoketone 5 in a solvent such as methanol or ethanol to provide intermediate 3f. Alternatively, for the preparation of intermediate 3f where R² is H, 2-bromo-dimethylacetal 6 and a catalytic amount of acid such as hydrochloric acid may be employed instead of intermediate 5. The conversion of 20 to 3f may also be carried out in two steps. First, aminopyrazine 20 and an appropriate bromide 5 are heated, conveniently in a solvent such as dioxane at 50 °C for 16 h. Then, solvent is removed, the residue treated with isopropanol, and the mixture heated at reflux for approximately 2 h to provide 3f.

25

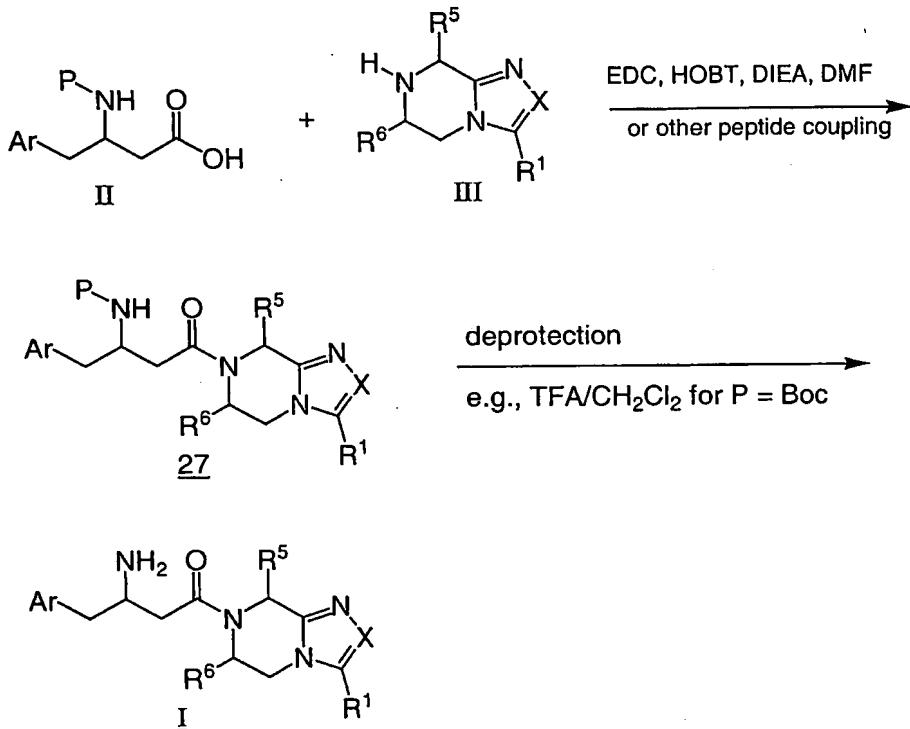
SCHEME 9

An alternate method for the preparation of Intermediate IIIa, wherein X is C-R² is illustrated in Scheme 9. Ring opening of epoxide 21, which is 5 commercially available, known in the literature or may be conveniently prepared by a variety of methods familiar to those skilled in the art, with azide, conveniently using ammonium chloride in the presence of sodium azide in DMF, gives azido alcohol 22. The alcohol is converted to the corresponding triflate, and treated with an N-benzyl alpha-amino acid ester, such as an ethyl ester, to provide amino ester 23. Aza-Wittig 10 reaction affords iminoether 24. Treatment with 3-aminopropyne according to the procedure of Maffrand et al., *Eur. J. Med. Chem.* 1975, 10, 528 gives tetrahydroimidazopyrazine 25, wherein R¹ is Me and R² is H, which may be 15 deprotected using ammonium formate in the presence of a palladium catalyst to give Intermediate IIIa. Alternatively, iminoether 24 may be converted to tetrahydroimidazopyrazine 25 by treatment with an alpha-aminoketone, following procedures outlined in Claxton et al., *J. Med. Chem.* 1974, 17, 364.

SCHEME 10



An alternate route to the preparation of Intermediate IIIb, wherein X is N, is illustrated in Scheme 10. Iminoether 24, from Scheme 10, is treated with a hydrazide in, for example, ethanol at 60°C , followed by heating in toluene at reflux, to give triazolopiperazine 26. Deprotection, for example, using ammonium formate in the presence of a palladium catalyst, affords Intermediate IIIb.

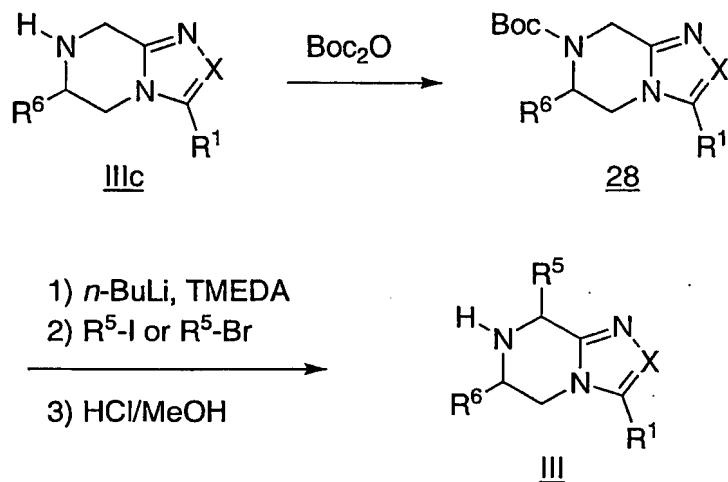
SCHEME 11

Intermediates II and III are coupled under standard peptide coupling conditions, for example, using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), 1-hydroxybenzotriazole (HOBT), and a base, generally diisopropylethylamine, in a solvent such as N,N-dimethylformamide (DMF) or dichloromethane for 3 to 48 hours at ambient temperature to provide intermediate 27 as shown in Scheme 11. The protecting group is then removed with, for example, trifluoroacetic acid or methanolic hydrogen chloride in the case of Boc to give the desired amine I. The product is purified from unwanted side products, if necessary, by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica, such as with a Biotage® apparatus, or HPLC. Compounds that are purified by HPLC may be isolated as the corresponding salt. Purification of intermediates is achieved in the same manner.

In some cases intermediates described in the above schemes may be further modified before removal of the protecting group, for example, by manipulation of substituents on X, R¹, R⁵, or R⁶. These manipulations may include,

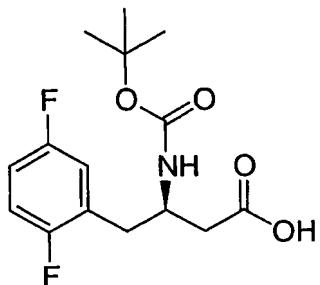
but are not limited to, reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

SCHEME 12



One such example is illustrated in Scheme 12. Intermediate IIIc, wherein R^5 is hydrogen, is protected, for example as its *tert*-butyl carbamate derivative by treatment with di-*tert*-butyl dicarbonate, to give heterocycle 28. This 10 derivative may be deprotonated with a strong base such as *n*-butyllithium in the presence of tetramethylethylenediamine. Treatment of the resultant anion with an alkyl halide followed by deprotection under acidic conditions provides the alkylated derivative III, which may be isolated as a salt, such as a hydrochloride salt.

In some cases the order of carrying out the foregoing reaction schemes 15 may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

INTERMEDIATE 1(3R)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(2,5-difluorophenyl)butanoic acid5 Step A. (R,S)-N-(1,1-Dimethylethoxycarbonyl)-2,5-difluorophenylalanine

To a solution of 0.5 g (2.49 mmol) of 2,5-difluoro-DL-phenylalanine in 5 mL of *tert*-butanol were added sequentially 1.5 mL of 2N aqueous sodium hydroxide solution and 543 mg of di-*tert*-butyl dicarbonate. The reaction was stirred at ambient temperature for 16 h and diluted with ethyl acetate. The organic phase was 10 washed sequentially with 1N hydrochloric acid and brine, dried over magnesium sulfate and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel, 97:2:1 dichloromethane:methanol:acetic acid) to afford 671 mg of the title compound. MS 302 (M + 1).

15 Step B. (R,S)-3-[(1,1-Dimethylethoxycarbonyl)amino]-1-diazo-4-(2,5-difluorophenyl)butan-2-one

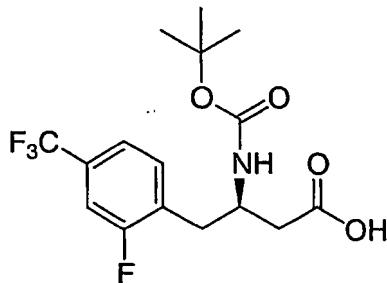
To a solution of 2.23 g (7.4 mmol) of (R,S)-N-(1,1-dimethylethoxycarbonyl)-2,5-difluorophenylalanine in 100 mL of diethyl ether at 0 °C were added sequentially 1.37 mL (8.1 mmol) of triethylamine and 0.931 mL (7.5 mmol) of isobutyl chloroformate and the reaction was stirred at this temperature for 15 min. A cooled ethereal solution of diazomethane was then added until the yellow color persisted and stirring was continued for a further 16 h. The excess diazomethane was quenched by dropwise addition of acetic acid, and the reaction was diluted with ethyl acetate and washed sequentially with 5% hydrochloric acid, 20 saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated in vacuo. Purification by flash chromatography (silica gel, 4:1 hexane:ethyl acetate) afforded 1.5 g of diazoketone. ¹H NMR (500 MHz,

CDCl₃) δ 7.03-6.95 (m, 1H), 6.95-6.88 (m, 2H), 5.43 (bs, 1H), 5.18 (bs, 1H), 4.45 (bs, 1H), 3.19-3.12 (m, 1H), 2.97-2.80 (m, 1H), 1.38 (s, 9H).

Step C. (3R)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(2,5-difluorophenyl)butanoic acid

5 To a solution of 2.14 g (6.58 mmol) of (R,S)-3-[(1,1-dimethylethoxycarbonyl)-amino]-1-diazo-4-(2,5-difluorophenyl)butan-2-one dissolved in 100 mL of methanol at -30 °C were added sequentially 3.3 mL (19 mmol) of diisopropylethylamine and 302 mg (1.32 mmol) of silver benzoate. The 10 reaction was stirred for 90 min before diluting with ethyl acetate and washing sequentially with 2N hydrochloric acid, saturated aqueous sodium bicarbonate, and brine. The organic phase was dried over magnesium sulfate, concentrated in vacuo and the enantiomers were separated by preparative chiral HPLC (Chiralpak AD column, 5% ethanol in hexanes) to give 550 mg of the desired (R)-enantiomer, which 15 eluted first. This material was dissolved in 50 mL of a mixture of tetrahydrofuran:methanol:1N aqueous lithium hydroxide (3:1:1) and stirred at 50 °C for 4 h. The reaction was cooled, acidified with 5% dilute hydrochloric acid and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated in vacuo to give 360 mg of the title 20 compound as a white foamy solid. ¹H NMR (500 MHz, CDCl₃) δ 7.21 (m, 1H), 6.98 (m, 2H), 6.10 (bs, 1H), 5.05 (m, 1H), 4.21 (m, 1H), 2.98 (m, 2H), 2.60 (m, 2H), 1.38 (s, 9H).

INTERMEDIATE 2



(3R)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-[2-fluoro-4-(trifluoromethyl)phenyl]butanoic acid

Step A. (2R,5S)-2,5-Dihydro-3,6-dimethoxy-2-(2'-fluoro-4'-trifluoromethyl)benzyl)-5-isopropylpyrazine

To a solution of 3.32 g (18 mmol) of commercially available (2S)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine in 100 mL of tetrahydrofuran at -70 °C was added 12 mL (19 mmol) of a 1.6M solution of butyllithium in hexanes. After stirring at this temperature for 20 min, 5 g (19.5 mmol) of 2-fluoro-4-trifluoromethylbenzyl bromide in 20 mL of tetrahydrofuran was added and stirring was continued for 3 h before warming the reaction to ambient temperature. The reaction was quenched with water, concentrated in vacuo, and extracted with ethyl acetate. The combined organic phase was washed with brine, dried, and concentrated in vacuo. Purification by flash chromatography (silica gel, 0-5% ethyl acetate in hexanes) afforded 5.5 g of the title compound. ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.25 (m, 3H), 4.35-4.31 (m, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 3.60 (t, 1H, J = 3.4 Hz), 3.33 (dd, 1H, J = 4.6, 13.5 Hz), 3.03 (dd, 1H, J = 7, 13.5 Hz), 2.25-2.15 (m, 1H), 1.0 (d, 3H, J = 7 Hz), 0.66 (d, 3H, J = 7 Hz).

Step B. (R)-N-(1,1-Dimethylethoxycarbonyl)-2-fluoro-4-(trifluoromethyl)phenylalanine methyl ester

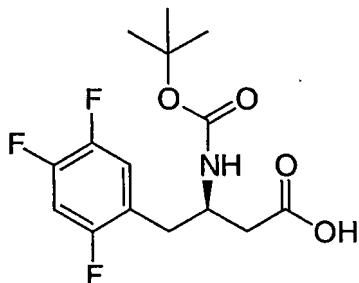
To a solution of 5.5 g (15 mmol) of (2R,5S)-2,5-dihydro-3,6-dimethoxy-2-(2'-fluoro-4'-(trifluoromethyl)benzyl)-5-isopropylpyrazine in 50 mL of a mixture of acetonitrile:dichloromethane (10:1) was added 80 mL of 1N aqueous trifluoroacetic acid. The reaction was stirred for 6 h and the organic solvents were removed in vacuo. Sodium carbonate was added until the solution was basic (>pH 8), and then the reaction was diluted with 100 mL of tetrahydrofuran and 10 g (46 mmol) of di-*tert*-butyl dicarbonate was added. The resultant slurry was stirred for 16 h, concentrated in vacuo, and extracted with ethyl acetate. The combined organic phase was washed with brine, dried, and concentrated in vacuo. Purification by flash chromatography (silica gel, 20% ethyl acetate in hexanes) afforded 5.1 g of the title compound. ^1H NMR (500 MHz, CDCl_3) δ 7.38-7.28 (m, 3H), 5.10 (bd, 1H), 4.65-3.98 (m, 1H), 3.76 (s, 3H), 3.32-3.25 (m, 1H), 3.13-3.05 (m, 1H), 1.40 (s, 9H).

Step C. (R)-N-(1,1-Dimethylethoxycarbonyl)-2-fluoro-4-(trifluoromethyl)phenylalanine

A solution of 5.1 g (14 mmol) of (*R,S*)-*N*-(1,1-dimethylethoxycarbonyl)-2-fluoro-4-(trifluoromethyl)phenylalanine methyl ester in 350 mL of a mixture of tetrahydrofuran: methanol:1N lithium hydroxide (3:1:1) was stirred at 50 °C for 4 h. The reaction was cooled, acidified with 5% dilute hydrochloric acid and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated in vacuo to give 4.8 g of the title compound. ^1H NMR (500 MHz, CD₃OD) δ 7.45-7.38 (m, 3H), 4.44-4.40 (m, 1H), 3.38-3.33 (m, 1H), 2.98 (dd, 1H, *J* = 9.6, 13.5 Hz), 1.44 (s, 9H).

5

10 **Step D.** (3*R*)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-[2-fluoro-4-(trifluoromethyl)phenyl]butanoic acid
To a solution of 3.4 g (9.7 mmol) of the product from Step C in 60 mL of tetrahydrofuran at 0 °C were added sequentially 2.3 mL (13 mmol) of *N,N*-diisopropylethylamine and 1.7 mL (13 mmol) of isobutyl chloroformate, and the 15 reaction was stirred at this temperature for 30 min. A cooled ethereal solution of diazomethane was then added until the yellow color persisted and stirring was continued for a further 16 h. The excess diazomethane was quenched by dropwise addition of acetic acid, and the reaction was diluted with ethyl acetate and washed sequentially with 5% hydrochloric acid, saturated aqueous sodium bicarbonate 20 solution and brine, dried over magnesium sulfate and concentrated in vacuo. Purification by flash chromatography (silica gel, 9:1 hexane:ethyl acetate) afforded 0.5 g of diazoketone. To a solution of 0.5 g (1.33 mmol) of the diazoketone dissolved in 100 mL of methanol at 0 °C were added sequentially 0.7 mL (4 mmol) of *N,N*-diisopropylethylamine and 32 mg (0.13 mmol) of silver benzoate. The reaction was 25 stirred for 2 h before diluting with ethyl acetate and washing sequentially with 2N hydrochloric acid, saturated aqueous sodium bicarbonate, and brine. The organic phase was dried over magnesium sulfate, concentrated in vacuo and dissolved in 50 mL of a mixture of tetrahydrofuran:methanol:1N aqueous lithium hydroxide (3:1:1) and stirred at 50 °C for 3 h. The reaction was cooled, acidified with 5% dilute 30 hydrochloric acid and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated in vacuo to give 410 mg of the title compound as a white foamy solid. ^1H NMR (500 MHz, CD₃OD) δ 7.47-7.33 (m, 3H), 4.88 (bs, 1H), 4.26-3.98 (m, 1H), 3.06-3.01 (m, 1H), 2.83-2.77 (m, 1H), 2.58-2.50 (m, 2H), 1.29 (s, 9H).

INTERMEDIATE 3(3R)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoic acid

5

Step A. (2S, 5R)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-(2',4',5'-trifluorobenzyl)pyrazine

The title compound (3.81 g) was prepared from 3.42 g (18.5 mmol) of (2S)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine and 5 g (22.3 mmol) of 2,4,5-trifluorobenzyl bromide using the procedure described for Intermediate 2, Step A. ¹H NMR (500 MHz, CDCl₃) δ 7.01 (m, 1H), 6.85 (m, 1H), 4.22 (m, 1H), 3.78 (m, 3H), 3.64 (m, 3H), 3.61 (m, 1H), 3.20 (m, 1H), 2.98 (m, 1H), 2.20 (m, 1H), 0.99 (d, 3H, J = 8 Hz), 0.62 (d, 3H, J = 8 Hz).

15

Step B. (R)-N-(1,1-Dimethylethoxycarbonyl)-2,4,5-trifluorophenylalanine methyl ester

To a solution of 3.81 g (11.6 mmol) of (2S, 5R)-2,5-dihydro-3,6-dimethoxy-2-isopropyl-5-(2',4',5'-trifluorobenzyl)pyrazine in 20 mL of acetonitrile was added 20 mL of 2N hydrochloric acid. The reaction was stirred for 72 h and concentrated in vacuo. The residue was dissolved in 30 mL of dichloromethane and 10 mL (72 mmol) of triethylamine and 9.68 g (44.8 mmol) of di-*tert*-butyldicarbonate were added. The reaction was stirred for 16 h, diluted with ethyl acetate and washed sequentially with 1N hydrochloric acid and brine. The organic phase was dried over sodium sulfate, concentrated in vacuo and purified by flash chromatography (silica gel, 9:1 hexanes:ethyl acetate) to afford 2.41 g of the title compound. ¹H NMR (500 MHz, CDCl₃) δ 6.99 (m, 1H), 6.94 (m, 1H), 5.08 (m, 1H), 4.58 (m, 1H), 3.78 (m, 3H), 3.19 (m, 1H), 3.01 (m, 1H), 1.41 (s, 9H).

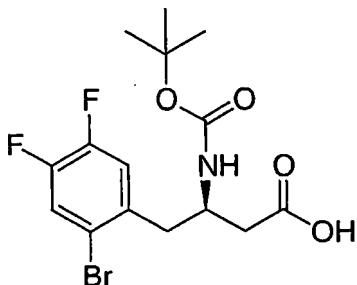
Step C. (R)-N-(1,1-Dimethylethoxycarbonyl)-2,4,5-trifluorophenylalanine

The title compound (2.01 g) was prepared from 2.41 g (7.5 mol) of (R)-N-(1,1-dimethylethoxycarbonyl)-2,4,5-trifluorophenylalanine methyl ester using the procedure described for Intermediate 2, Step C. MS (M + 1 - BOC) 220.9.

5

Step D. (3R)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)-butanoic acid

To a solution of 0.37 g (1.16 mmol) of (R)-N-(1,1-dimethylethoxycarbonyl)-2,4,5-trifluorophenylalanine in 10 mL of diethyl ether at -20 °C were added sequentially 0.193 mL (1.3 mmol) of triethylamine and 0.18 mL (1.3 mmol) of isobutyl chloroformate, and the reaction was stirred at this temperature for 15 min. A cooled ethereal solution of diazomethane was then added until the yellow color persisted and stirring was continued for a further 1 h. The excess diazomethane was quenched by dropwise addition of acetic acid, and the reaction was diluted with ethyl acetate and washed sequentially with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated in vacuo. Purification by flash chromatography (silica gel, 3:1 hexane:ethyl acetate) afforded 0.36 g of diazoketone. To a solution of 0.35 g (1.15 mmol) of the diazoketone dissolved in 12 mL of 1,4-dioxane: water (5:1) was added 26 mg (0.113 mmol) of silver benzoate. The resultant solution was sonicated for 2 h before diluting with ethyl acetate and washing sequentially with 1N hydrochloric acid and brine, drying over magnesium sulfate and concentrating in vacuo. Purification by flash chromatography (silica gel, 97:2:1 dichloromethane:methanol:acetic acid) afforded 401 mg of the title compound. ¹H NMR (500 MHz, CDCl₃) δ 7.06 (m, 1H), 6.95 (m, 1H), 5.06 (bs, 1H), 4.18 (m, 1H), 2.98 (m, 2H), 2.61 (m, 2H), 1.39 (s, 9H).

INTERMEDIATE 4(3R)-4-(2-Bromo-4,5-difluorophenyl)-3-[(tert-butoxycarbonyl)amino]butanoic acid

To a solution of 2.4 g (10 mmol) of 2-bromo-4,5-difluorobenzoic acid

5 [prepared according to the procedure of Braish et al., *Syn. Comm.*, 3067-3074 (1992)] in 75 mL of tetrahydrofuran was added 2.43 g (15 mmol) of 1,1'-carbonyldiimidazole. The solution was heated under reflux for 3.5 h, cooled to ambient temperature and 0.38 g (10 mmol) of sodium borohydride in 15 mL of water was added. The reaction was stirred for 10 min and partitioned between ethyl acetate and 10% aqueous sodium

10 bicarbonate solution. The organic layer was washed twice with warm water, brine, dried over magnesium sulfate, and concentrated in vacuo. Purification by flash chromatography (silica gel, 4:1 hexane:ethyl acetate) afforded 1.9 g of 2-bromo-4,5-difluorobenzyl alcohol. To a solution of 1.9 g (8.4 mmol) of 2-bromo-4,5-difluorobenzyl alcohol in 30 mL of dichloromethane at 0 °C was added 3.4 g (10 mmol) of carbon tetrabromide and 2.7 g (10 mmol) of triphenylphosphine. The

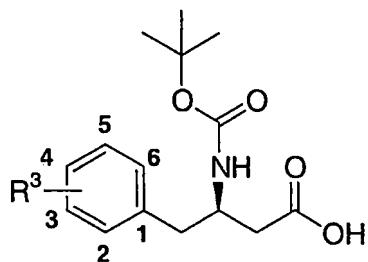
15 reaction was stirred for 2 h at this temperature, the solvent was removed in vacuo and the residue stirred with 100 mL of diethyl ether. The solution was filtered, concentrated in vacuo, and purified by flash chromatography (silica gel, 20:1 hexane:ethyl acetate) to afford 2.9 g of 2-bromo-4,5-difluorobenzyl bromide

20 contaminated with carbon tetrabromide which was used without further purification. Using the procedures outlined for the preparation of Intermediates 1-3, the benzyl bromide derivative was converted to the title compound.

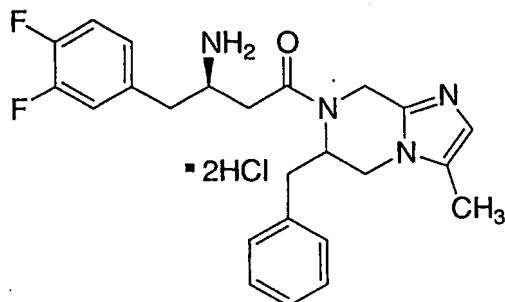
LC/MS 394 and 396 (M+1).

25 Essentially following the procedures outlined for the preparation of Intermediates 1-4, the Intermediates in Table 1 were prepared.

TABLE 1



Intermediate	R ³	Selected ¹ H NMR data (CD ₃ OD)
5	2-F,4-Cl,5-F	7.11 (dd, 1 H, J = 8.9, 6.4 Hz), 7.03 (dd, 1 H, J = 9.0, 6.6)
6	2-F,5-Cl	7.27 (dd, 1 H, J = 6.4, 2.5 Hz), 7.21 (m, 1 H), 7.03 (t, 1 H, J = 9.2 Hz)
7	2-Me,5-Cl	7.16 (d, 1 H, J = 1.8 Hz), 7.11-7.07 (m, 2 H), 2.34 (s, 3 H)
8	2-Cl,5-Cl	7.34 (d, 1 H, J = 9.0), 7.33 (d, 1 H, J = 2.1 Hz), 7.21 (dd, 1 H, J = 8.5, 2.5 Hz)
9	2-F,3-Cl,6-F	7.35 (td, 1 H, J = 8.5, 5.8 Hz), 6.95 (t, 1 H, J = 8.5 Hz)
10	3-Cl,4-F	7.33 (d, 1 H, J = 6.9 Hz), 7.19-7.11 (m, 2 H)
11	2-F,3-F,6-F	7.18-7.12 (m, 1 H), 6.91 (m, 1 H)
12	2-F,4-F,6-F	6.81 (t, 2 H, J = 8.4 Hz)
13	2-OCH ₂ Ph,5-F	7.49 (d, 2 H, J = 7.6 Hz), 7.38 (t, 2 H, J = 7.3 Hz), 7.30 (t, 1 H, J = 7.3 Hz), 6.96-6.89 (m, 3 H), 5.11 (d, 1 H, J = 11.7 Hz), 5.08 (d, 1 H, J = 11.9 Hz)

EXAMPLE 1

5 7-[(3R)-3-Amino-4-(3,4-difluorophenyl)butanoyl]-3-methyl-6-(phenylmethyl)-5,6,7,8-
tetrahydroimidazo[1,2-a]pyrazine, dihydrochloride

10 Step A. 1-Azido-3-phenyl-2-propanol
To a mixture of 24.22 g (372.5 mmol) of sodium azide and 19.93 g (372.5 mmol) of ammonium chloride in 150 mL of DMF was added 10.0 g (74.5 mmol) of 2-benzyloxirane. The reaction mixture was stirred at 100 °C for 18 h and then partitioned between water and ethyl acetate. The aqueous phase was extracted with two portions of ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated to give 13.4 g of a viscous oil. Purification by flash chromatography (silica gel, eluting sequentially with 4:1 hexane/ethyl acetate and 1:1 hexane ethyl acetate) gave 10.5 g of the title compound. TLC (R_f = 0.41 in 4 : 1 hexanes/ethyl acetate); 1 H NMR (500 MHz, CDCl₃) δ 7.37 (t, 2H, J=7.6 Hz), 7.30 (t, 1H, J=6.4 Hz), 7.25 (t, 2H, J=7.3 Hz), 4.01~4.06 (m, 1H), 3.31~3.43 (m, 2H), 2.81~2.88 (m, 2H), 2.12 (s, 1H).

15 Step B. Ethyl N-(1-Azido-3-phenylprop-2-yl)-N-(phenylmethyl)-2-aminoacetate
To a solution of 8.285 g (46.78 mmol) of azidoalcohol from Step A and 10.9 mL (10.026 g, 93.56 mmol) of 2,6-lutidine in 50 mL of dichloromethane at 0 °C was added 7.87 mL (13.2 g, 46.78 mmol) of triflic anhydride. The reaction mixture was stirred at 0 °C for 15 min and then 18.08 g (93.56 mmol) of ethyl N-(phenylmethyl)-2-aminoacetate were added. The resultant mixture was stirred at 0 °C for 20 min and at ambient temperature for 90 min. The mixture was partitioned

between dichloromethane and saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted with three portions of dichloromethane. The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (silica gel, 9:1 hexane/ethyl acetate) gave 4.596 g of the title compound as a yellow viscous oil. MS 353 (M+1).

5 Step C. 5-Ethoxy-1,2-bis(phenylmethyl)-1,2,3,6-tetrahydropyrazine
A mixture of 2.50 g (7.10 mmol) of ethyl ester from Step B and 1.863 g (7.10 mmol) of triphenylphosphine in 20 mL of toluene was heated at 100 °C for 18
10 h. The reaction mixture was cooled to ambient temperature and partitioned between ethyl acetate and water. The aqueous phase was extracted with three portions of ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (silica gel, eluting sequentially with 9:1, 4:1 then 1:1 hexane/ethyl acetate) gave 198 mg of the title
15 compound. MS 309 (M+1).

Step D. 3-Methyl-6,7-bis(phenylmethyl)-5,6,7,8-tetrahydroimidazo[1,2-
a]pyrazine
A mixture of 195 mg (0.633 mmol) of the compound from Step C and 0.13 mL (104.6 mg, 1.90 mmol) of 3-amino-1-propyne in 2 mL of toluene was heated at 100 °C for 18 h and then concentrated. Purification by flash chromatography (silica gel, eluting sequentially with 1:1 hexane/ethyl acetate, 100% ethyl acetate, 10% methanol/dichloromethane) gave 116 mg of the title compound as a brown, viscous oil. MS 318 (M+1).

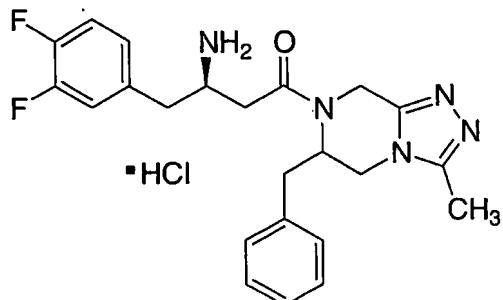
25 Step E. 3-Methyl-6-(phenylmethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine
To a solution of 410 mg (1.293 mmol) of tetrahydroimidazopyrazine from Step D in 10 mL of ethanol was added 410 mg of ammonium formate and 200 mg of 10% palladium on carbon. The reaction mixture was heated at reflux
30 temperature under an atmosphere of hydrogen for 4 h. The mixture was then filtered through Celite and concentrated. Purification by flash chromatography (silica gel, 10% methanol/dichloromethane) gave 212 mg of the title compound as a glass. MS 228 (M+1).

Step F. 7-[(3R)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)butanoyl]-3-methyl-6-(phenylmethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine

To a solution of 93.3 mg (0.30 mmol) of 3-methyl-6-(phenylmethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine from Step E, 85 mg (0.27 mmol) of (3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)butanoic acid, and 0.0454 mL (32.8 mg, 0.32 mmol) of diisopropylethylamine in 2 mL of THF was added 132.7 mg (0.30 mmol) of benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP). The reaction was stirred at ambient temperature for 18 h and then concentrated and partitioned between ethyl acetate and water. The aqueous phase was extracted with three portions of ethyl acetate. The combined organic phase was washed with brine, dried over magnesium sulfate, and concentrated. Purification by preparative TLC (silica gel, 10% methanol/dichloromethane) gave 130 mg of the title compound as a pale yellow powder, which was further purified by HPLC (Gilson; YMC-Pack Pro C18 column, 100 x 20 mm I.D.; solvent gradient from 10% acetonitrile, 90% water, and 0.1 % trifluoroacetic acid to 90% acetonitrile, 10% water, and 0.1 % trifluoroacetic acid) to give 101 mg of the title compound as solid. MS 525 (M+1).

20 Step G. 7-[(3*R*)-3-Amino-4-(3,4-difluorophenyl)butanoyl]-3-methyl-6-(phenylmethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, dihydrochloride

A solution of 30 mg of 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)butanoyl]-3-methyl-6-(phenylmethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine from Step F in 2 mL of 4 N hydrogen chloride in dioxane was stirred at ambient temperature for 2 h. Concentration gave 18 mg of the title compound. MS 425 (M+1).

EXAMPLE 2

7-[(3R)-3-Amino-4-(3,4-difluorophenyl)butanoyl]-3-methyl-6-(phenylmethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, dihydrochloride

5

Step A. 3-Methyl-N,6-bis(phenylmethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine

To a solution of 628 mg (2.039 mmol) of 5-ethoxy-1,2-bis(phenylmethyl)-1,2,3,6-tetrahydropyrazine from Example 1, Step C in 15 mL of ethanol was added 181.3 mg (2.447 mmol) of acetic hydrazide. The mixture was stirred at 60 °C for 14 h and then concentrated. The resultant brown viscous oil was dissolved in toluene and heated at reflux for 5 h. The mixture was concentrated. Purification by flash chromatography (silica gel, eluting sequentially with ethyl acetate then 10% methanol/dichloromethane) gave 486 mg of the title compound. MS 15 319 (M+1).

Step B. 3-Methyl-6-(phenylmethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine

To a solution of 440 mg (1.384 mmol) of 3-methyl-N,6-bis(phenylmethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a] pyrazine from Step A and 440 mg of ammonium formate in 10 mL of ethanol was added 440 mg of 10% palladium on carbon. The reaction mixture was heated at 80 °C under an atmosphere of hydrogen for 4 h. The mixture was then filtered through Celite and concentrated. Purification by flash chromatography (silica gel, eluting sequentially with 10% methanol/dichloromethane then 80:15:1 chloroform/methanol/ammonium hydroxide) gave 105 mg of the title compound as a white solid. MS 229 (M+1).

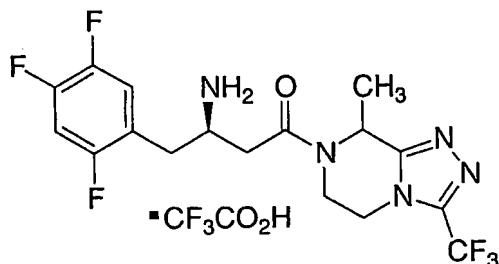
Step C. 7-[(3R)-3-[(1,1-Dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)butanoyl]-3-methyl-6-(phenylmethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine

To a solution of 12 mg (0.053 mmol) of 3-methyl-6-(phenylmethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine from Step B, 16.6 mg (0.053 mmol) of (3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)butanoic acid, and 8.6 mg (0.0636 mmol) of HOBT in 3 mL of dichloromethane was added 15.3 mg (0.080 mmol) of EDC and 0.0186 mL (13.4 mg, 0.183 mmol) of diisopropylethylamine. The reaction was stirred at ambient temperature for 18 h and then concentrated and partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The aqueous phase was extracted with three portions of dichloromethane. The combined organic phase was washed with brine, dried over magnesium sulfate, and concentrated. Purification by preparative TLC (silica gel, 10% methanol/dichloromethane) gave 10.1 mg of the title compound as a viscous oil.

15 MS 470 (M+1-tBu).

Step D. 7-[(3*R*)-3-Amino-4-(3,4-difluorophenyl)butanoyl]-3-methyl-6-(phenylmethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine, hydrochloride

20 A solution of 9.0 mg of 7-[(3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)butanoyl]-3-methyl-6-(phenylmethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine from Step C in 2 mL of 4 N hydrogen chloride in dioxane was stirred at ambient temperature for 1 h. Concentration gave 9.2 mg of the title compound. MS 426 (M+1).

EXAMPLE 3

7-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-8-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, trifluoroacetate salt

5

Step A. 2-Hydrazino-3-methylpyrazine

To 15 mL of hydrazine hydrate at ambient temperature was added dropwise 5 g (42.9 mmol) of 2-chloro-3-methylpyrazine. The resultant mixture was heated to 120 °C for 45 min then cooled in a refrigerator for 48 h. The yellow precipitate was collected by vacuum filtration and dried under vacuum to give 1.6 g (30%) of the title compound which was used without further purification. ¹H NMR (400 MHz, CD₃OD) δ 7.94 (d, 1H, J=3.0 Hz), 7.63 (d, 1H, J=3.0 Hz), 2.32 (s, 3H).

15

Step B. N-(3-Methylpyrazin-2-yl)-2,2,2-trifluoroacetohydrazide

To 1.6 g (12.9 mmol) of the product from Step A at 0 °C was added slowly and with vigorous stirring 16 mL of trifluoroacetic anhydride that had been cooled to 0 °C. The resultant mixture was stirred at ambient temperature for 1 h, concentrated in vacuo, and made basic by treatment with methanolic ammonia. The residue was purified by column chromatography (silica gel, 5% methanol/ 0.5% ammonium hydroxide/ dichloromethane) to give 2.83 g (100%) of the title compound. MS 221 (M+1).

25

Step C. 8-Methyl-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine

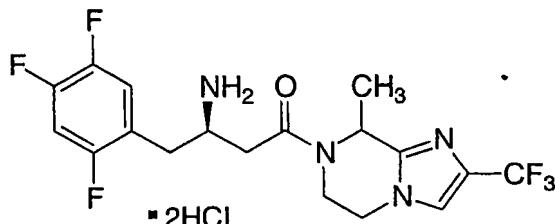
To 2.8 g (12.9 mmol) of the product from Step B was added

approximately 10 mL of polyphosphoric acid and the resultant mixture was heated at 140 °C for 16 h. The dark mixture was poured into ice, basified to pH 9 with 29% ammonium hydroxide, and extracted into ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, concentrated in vacuo and the residue

purified by column chromatography (silica gel, 30 % ethyl acetate/hexane) to give 815 mg (31%) of the title compound. MS 203 (M+1).

5 Step D. 8-Methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine
To a solution of 400 mg (1.98 mmol) of the product from Step C in 10 mL of ethanol was added 231 mg of 10% palladium on activated carbon and the mixture stirred under 1 atmosphere of hydrogen at ambient temperature for 16 h. The solution was filtered through Celite and the filtrate concentrated in vacuo to give 390 mg (96%) of the title compound which was used without further purification. MS 207 (M+1).

10 Step E. 7-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-8-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, trifluoroacetate salt
15 To a solution of 200 mg (0.97 mmol) of the product from Step D in 5 mL of dimethylformamide was added 280 mg (0.84 mmol) of (3R)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoic acid, 198 mg (1.45 mmol) of 1-hydroxy-7-azabenzotriazole (HOAT), 0.422 mL (2.4 mmol) of N,N-diisopropylethylamine, and 443 mg (1.2 mmol) of O-(7-azabenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU). After stirring at ambient temperature for 16 h, the mixture was diluted with ethyl acetate and the organic layer washed sequentially with one portion of saturated aqueous sodium bicarbonate solution, three portions of water, and one portion of brine. The organic layer was 20 dried over magnesium sulfate, concentrated, and the residue purified by preparative TLC (silica gel, 75% ethyl acetate/hexane) to give 86 mg of the N-BOC-protected title compound as a mixture of diastereomers. Chiral HPLC separation (ChiralCel OJ or ChiralCel OD column, 10% ethanol/hexane) provided the individual diastereomers, each of which were treated with a 1:1 mixture of trifluoroacetic acid and 25 dichloromethane at ambient temperature. Removal of the excess trifluoroacetic acid by azeotropic distillation with dichloromethane and methanol provided 24.3 mg of each diastereomer of the title compound. Faster eluting diastereomer: MS 422 (M+1); slower eluting diastereomer: MS 422 (M+1).

EXAMPLE 4

7-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-8-methyl-2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine, dihydrochloride

5

Step A. 8-Chloro-2-(trifluoromethyl)-2,3-dihydroimidazo[1,2-a]pyridin-2-ol, hydrobromide

To a suspension of 5.58 g (43.1 mmol) of 2-amino-3-chloropyrazine in 55 mL of dioxane was added slowly 6.7 mL (64.5 mmol) 3-bromo-1,1,1-trifluoroacetone. The reaction mixture was heated at 50 °C overnight. The resultant precipitate was collected by filtration and washed with diethyl ether to provide, after drying under vacuum, 12.62 g of a grayish solid that was used without further purification.

15 Step B. 8-Chloro-2-(trifluoromethyl)imidazo[1,2-a]pyrazine

A 9.62 g portion of hydrobromide from Step A was free-based by treatment with 5 N aqueous sodium hydroxide solution. Extraction into ethyl acetate, drying over magnesium sulfate and concentration gave 6.2 g (25.9 mmol) of alcohol which was heated to reflux in 250 mL of isopropanol. After 4 h the reaction was complete as judged by TLC analysis. The mixture was concentrated in vacuo and the residue suspended in ethyl acetate, washed with saturated sodium bicarbonate solution, dried over magnesium sulfate and concentrated. Purification by Biotage chromatography (silica gel, 20% ethyl acetate/hexane) gave 3.96 g of the title compound. MS 222 (M+1).

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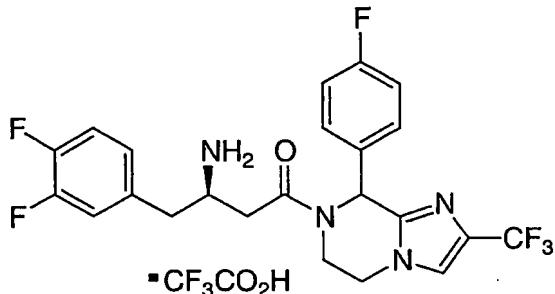
Step C. 8-Methyl-2-(trifluoromethyl)imidazo[1,2-a]pyrazine

This reaction was carried out following the procedure described in *J. Org. Chem.* 1987, 52, 3847. A suspension of 3.88 g (27.05 mmol) of copper(I) bromide in 30 mL of anhydrous THF was cooled to -78 °C. A solution of

methylmagnesium bromide (18 mL, 54 mmol, 3.0 M in diethyl ether) was added and the mixture was stirred at -78 °C for 30 min. To this was added dropwise a solution of 1.5 g (6.77 mmol) of imidazopyrazine from Step B in 30 mL of anhydrous THF and the mixture was stirred at -78 °C for 2 h. The reaction mixture was allowed to 5 warm to -70 °C over 1 h, and then was stirred at ambient temperature for 3 h. The reaction was quenched by the addition of 29% ammonium hydroxide solution and extracted with ethyl acetate. The organic phase was washed sequentially with aqueous ammonium hydroxide and brine, dried over magnesium sulfate, and concentrated. Purification by Biotage chromatography (silica gel, 25% ethyl 10 acetate/hexane) gave 690 mg of the title compound. MS 202 (M+1).

Step D. 8-Methyl-2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine
Imidazopyrazine from Step C (690 mg, 3.43 mmol) in approximately 20 mL of ethanol was stirred with 400 mg of 10% palladium on carbon under an 15 atmosphere of hydrogen for 16 h. The mixture was filtered through Celite and concentrated to give 670 mg of the title compound which was used without further purification.

Step E. 7-[(3*R*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-8-methyl-2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, dihydrochloride
A mixture of 670 mg (3.3 mmol) of tetrahydroimidazo[1,2-*a*]pyrazine from Step D, 1.3 g (3.9 mmol) of (3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(2,3,5-trifluorophenyl)butanoic acid, 1.51 g (3.97 mmol) of HATU, 674 mmol (4.95 20 mmol) of HOAT, and 1.44 mL (8.3 mmol) of diisopropylethylamine in 10 mL of DMF was stirred at ambient temperature for 16 h. The reaction mixture was diluted with ethyl acetate, washed sequentially with saturated aqueous sodium bicarbonate solution, four portions of water, and brine, dried over magnesium sulfate, and concentrated. Purification by Biotage chromatography (silica gel, 30% ethyl 25 acetate/hexane) gave 1.62 g of the Boc protected derivative as two diastereomers, which were then separated by chromatography on a ChiralCel OJ column (10% ethyl acetate/hexane) to give 640 mg of the faster eluting diastereomer and 700 mg of the slower eluting diastereomer. Each diastereomer was deprotected separately by treatment with methanolic hydrogen chloride at ambient temperature for 1.5 h to give 30 35 two diastereomers of the title compound. MS 421 (M+1)

EXAMPLE 5

7-[(3R)-3-Amino-4-(3,4-difluorophenyl)butanoyl]-8-(4-fluorophenyl)-2-

5 (trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine, trifluoroacetate salt

Step A. 8-(4-Fluorophenyl)-2-(trifluoromethyl)imidazo[1,2-a]pyrazine

A mixture of 150 mg (0.68 mmol) of 8-chloro-2-(trifluoromethyl)imidazo[1,2-a]pyrazine (Example 4, Step B) and 190 mg (1.36 mmol) of 4-fluorophenylboronic acid, 0.931 mL of 2 M aqueous sodium carbonate solution and 0.233 mL of ethanol was heated at 80 °C under an atmosphere of nitrogen for 16 h. The mixture was diluted with ethyl acetate, washed sequentially with saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulfate and concentrated. Purification by preparative TLC (silica gel, 30% ethyl acetate/hexane) provided 134 mg of the title compound. MS 282 (M+1).

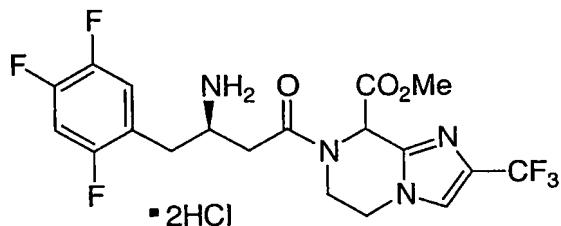
Step B. 8-(4-Fluorophenyl)-2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine

Imidazopyrazine from Step A (134 mg, 0.48 mmol) in 8 mL of ethanol was stirred with 53 mg of 10% palladium on carbon under an atmosphere of hydrogen for 16 h. The mixture was filtered through Celite and concentrated in vacuo. Purification by preparative TLC (silica gel, 5% methanol/dichloromethane) gave 106 mg of the title compound as a white solid. MS 286 (M+1).

25 Step C. 7-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-8-(4-fluorophenyl)-2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine, trifluoroacetate salt

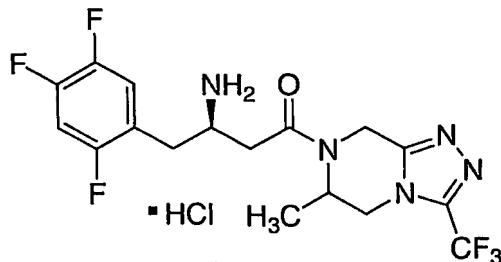
The tetrahydroimidazopyrazine from Step B (30 mg, 0.11 mmol) was coupled with (3*R*)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(3,4-difluorophenyl)-butanoic acid following the procedure outlined in Example 4, Step E. Purification by preparative TLC (silica gel, 50% ethyl acetate hexane) gave 65 mg of the Boc intermediate as a mixture of diastereomers, which were separated by chromatography using a ChiralPak AD column (14% ethanol/hexanes). Each was deprotected separately by treatment with 1:1 trifluoroacetic acid/dichloromethane to give 19.8 mg of the title compound from the faster eluting diastereomer and 19.7 mg of title compound from the slower eluting diastereomer. MS 483 (M+1).

10

EXAMPLE 6

7-[(3*R*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-8-(methoxycarbonyl)-2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazine, dihydrochloride

15 Methyl 3-aminopyrazine-2-carboxylate was converted to the title compound, as a mixture of diastereomers, essentially following the procedures outlined in Example 4, Steps A, B, D and E. MS 465 (M+1).

EXAMPLE 7

20

7-[(3*R*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine, hydrochloride

Step A. 2-Hydroxy-5-methylpyrazine

To a solution of 10.1 g (80.9 mmol) of L-alanine amide hydrochloride in 100 mL of methanol and 100 mL of water at -40 °C was added 9.28 mL of aqueous glyoxal (40 wt %) dropwise. The mixture was stirred at -40 °C for 5 min, then 10 mL of 50% aqueous sodium hydroxide was added. The resultant mixture was allowed to stir at room temperature for 18 h. The solution was cooled to 0 °C and 12 mL of concentrated hydrochloric acid were added, followed by 15 g of sodium bicarbonate. The mixture was stirred at room temperature for 5 min, and then an additional 15 g of sodium bicarbonate was added. After stirring for 20 min, the mixture was filtered.

10 The filtrate was concentrated to give a yellow solid. To this solid was added 500 mL of 80:15:1 dichloromethane/methanol/ammonium hydroxide and the mixture was stirred vigorously. A yellow solid was removed by filtration, and the filtrate was concentrated to give the title compound. MS 110.9 (M+1).

15 Step B. 2-Chloro-5-methylpyrazine

A 250-mL round bottom flask was charged with 8.61 g of 2-hydroxy-5-methylpyrazine from Step A and 50 mL of phosphorus oxychloride. After the addition of 0.2 mL of sulfuric acid, the mixture was heated at reflux for 1 h. An additional 2.5 mL of sulfuric acid was added and the resultant solution was heated at reflux for 14 h, and then concentrated in vacuo. The residue was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The aqueous phase was extracted with three portions of ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. Purification by flash chromatography (silica gel, 4:1 then 1:1 hexane/ethyl acetate) afforded the title compound as a yellow oil. MS 128.9 (M+1).

Step C. 2-Hydrazino-5-methylpyrazine

The title compound was prepared from 3.99 g of 2-chloro-5-methylpyrazine essentially following the procedure outlined in Example 3, Step A.

30 MS 124.9 (M+1).

Step D. N-(5-Methylpyrazin-2-yl)-2,2,2-trifluoroacetohydrazide

The title compound was prepared from 2.94 g of 2-hydrazino-5-methylpyrazine essentially following the procedure outlined in Example 3, Step B,

except the reaction mixture was concentrated in vacuo and the product used in Step E without further purification. MS 221 (M+1).

Step E. 6-Methyl-3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*]pyrazine

5 To the product from Step D was added 30 mL of superphosphoric acid and the resultant mixture was heated at 120 °C for 4 h. The mixture was cooled to room temperature, poured into ice, basified with 29% ammonium hydroxide, and extracted with three portions of ethyl acetate. The combined organic phase was washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The 10 residue was purified by column chromatography (silica gel, 50 % ethyl acetate/hexane) to give the title compound. MS 202.9 (M+1).

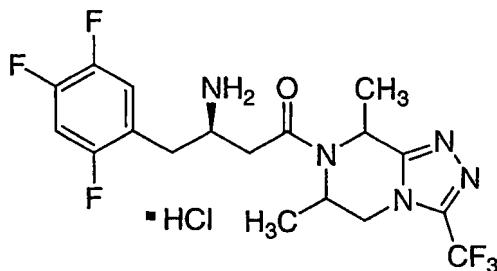
Step F. 6-Methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine

15 The title compound was prepared from 2.65 g of the product from Step E, essentially following the procedure outlined in Example 3, Step D. Purification by flash chromatography (silica gel, 10% methanol/dichloromethane) gave the title compound as a solid. MS 207 (M+1).

20 Step G. 7-[(3*R*)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine, hydrochloride

25 The title compound was prepared from 509 mg of the product from Step F, essentially following the procedure outlined in Example 3, Step D. The reaction mixture was stirred for 3 d prior to work-up. Flash chromatography (silica gel, 50% ethyl acetate/hexane) gave the coupled product as a mixture of C-6 diastereomers. Chiral HPLC separation (ChiralCel OD column, 15% ethanol/hexane) provided the individual diastereomers, each of which was treated with a 1:1 mixture of methanol and saturated methanolic hydrogen chloride at ambient temperature for 1 30 h. Concentration provided each diastereomer of the title compound. Faster eluting diastereomer: MS 422 (M+1); slower eluting diastereomer: MS 422 (M+1).

EXAMPLE 8



7-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-6,8-dimethyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, hydrochloride

5 Step A. 7-(1,1-Dimethylethoxycarbonyl)-6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine

To a solution of 1.74 g (8.45 mmol) of 6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine from Example 7, Step F in 40 mL of dichloromethane was added 2.03 g (9.29 mmol) of di-*tert*-butyl dicarbonate. The 10 reaction mixture was stirred at room temperature for 18 h. Concentration gave the title compound. MS 307 (M+1).

Step B. 7-(1,1-Dimethylethoxycarbonyl)-6,8-dimethyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine

15 To a solution of 2.17 g (7.11 mmol) of the product from Step A in 25 mL of toluene at -78 °C was added 1.13 mL (7.47 mmol) of tetramethylethylenediamine and 3.0 mL (7.47 mmol) of 2.5M *n*-butyllithium solution in hexane. The reaction mixture was stirred for 10 min and then 0.465 mL (7.47 mmol) of iodomethane was added dropwise at -78 °C. The reaction mixture was 20 stirred for 10 min, and then allowed to gradually warm to room temperature. The reaction was quenched by the addition of aqueous ammonium chloride solution and extracted with three portions of ethyl acetate. The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated. Purification by flash chromatography (silica gel, 0 to 10% methanol/dichloromethane gradient 25 elution) gave the title compound as a mixture of diastereomers. MS 321 (M+1), 265 (M+1-BOC).

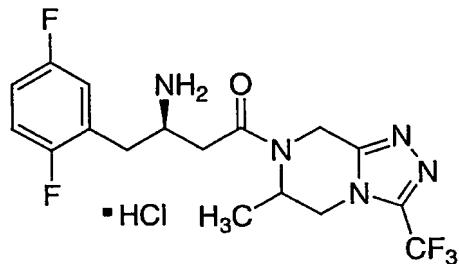
Step C. 6,8-Dimethyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, hydrochloride

The product from Step B was dissolved in saturated methanolic hydrogen chloride. The solution was stirred at room temperature for 1 h. Concentration gave the title compound. MS 207 (M+1).

5 **Step D.** 7-[(3R)-3-Amino-4-(2,4,5-trifluorophenyl)butanoyl]-6,8-dimethyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, hydrochloride

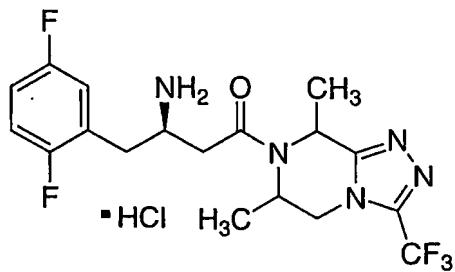
The title compound is prepared by coupling the product from Step C with (3R)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoic acid (Intermediate 3). Treatment of the coupled product with methanolic hydrogen chloride provides the title compound.

EXAMPLE 9



15 7-[(3R)-3-Amino-4-(2,5-difluorophenyl)butanoyl]-6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, hydrochloride

The title compound is prepared by coupling 6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine from Example 7, Step F with (3R)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(2,5-difluorophenyl)butanoic acid (Intermediate 1). Treatment of the coupled product with methanolic hydrogen chloride provides the title compound.

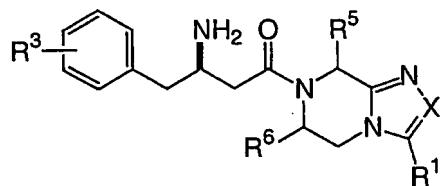
EXAMPLE 107-[(3R)-3-Amino-4-(2,5-difluorophenyl)butanoyl]-6,8-dimethyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, hydrochloride

5 The title compound is prepared by coupling 6,8-dimethyl-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a]pyrazine, hydrochloride from Example 8, Step C with (3R)-3-[(1,1-dimethylethoxycarbonyl)amino]-4-(2,5-difluorophenyl)butanoic acid (Intermediate 1). Treatment of the coupled product with methanolic hydrogen chloride provides the title compound.

10

Essentially following the procedures outlined for Examples 1-10, the compounds listed in Table 2 were prepared.

TABLE 2



Ex.	R ³	R ⁵	R ⁶	X	R ¹	MS (M+1)
11	2-F,5-F	4-F-Ph (diast 1)	H	C-CF ₃	H	483
12	2-F,5-F	4-F-Ph (diast 2)	H	C-CF ₃	H	483
13	2-F	3-CF ₃ -Ph (diast 1)	H	C-CF ₃	H	515
14	2-F	3-CF ₃ -Ph (diast 2)	H	C-CF ₃	H	515
15	2-F,5-F	Me (diast 1)	H	C-CF ₃	H	403
16	2-F,5-F	Me (diast 2)	H	C-CF ₃	H	403
17	2-F,5-F	Et (diast 1)	H	C-CF ₃	H	417
18	2-F,5-F	Et (diast 2)	H	C-CF ₃	H	417
19	2-F,5-F	Isopropyl (diast 1)	H	C-CF ₃	H	431
20	2-F,5-F	Isopropyl (diast 2)	H	C-CF ₃	H	431
21	3-F,4-F	H	4-F-Ph	C-CF ₃	H	483

22	2-F	H	4-F-Ph	C-CF ₃	H	465
23	2-F,5-F	H	Me (diast 1)	C-CF ₃	H	403
24	2-F,5-F	H	Me (diast 2)	C-CF ₃	H	403
25	2-F,5-F	H	3-CF ₃ -Ph (diast 1)	C-CF ₃	H	533
26	2-F,5-F	H	3-CF ₃ -Ph (diast 2)	C-CF ₃	H	533
27	2-F,4-F,5-F	Et (diast 1)	H	N	CF ₃	436
28	2-F,4-F,5-F	Et (diast 2)	H	N	CF ₃	436
29	2-F,5-F	Me (diast 1)	H	N	CF ₃	404
30	2-F,5-F	Me (diast 2)	H	N	CF ₃	404

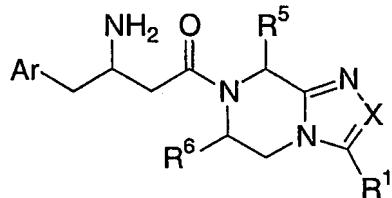
EXAMPLE OF A PHARMACEUTICAL FORMULATION

As a specific embodiment of an oral pharmaceutical composition, a 100 mg potency tablet is composed of 100 mg of any of the compounds of the present invention, 268 mg microcrystalline cellulose, 20 mg of croscarmellose sodium, and 4 mg of magnesium stearate. The active, microcrystalline cellulose, and croscarmellose are blended first. The mixture is then lubricated by magnesium stearate and pressed into tablets.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. The specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of the formula I:



5

wherein:

Ar is phenyl which is unsubstituted or substituted with 1-5 of R³, wherein R³ is independently selected from the group consisting of:

- (1) halogen,
- (2) C₁₋₆ alkyl, which is linear or branched and is unsubstituted or substituted with 1-5 halogens,
- (3) C₁₋₆ alkoxy, which is linear or branched and is unsubstituted or substituted with 1-5 halogens,
- (4) CN, and
- (5) hydroxy;

X is selected from the group consisting of:

- (1) N and
- (2) CR²;

20

R¹ and R² are each independently selected from the group consisting of:

- (1) hydrogen,
- (2) CN,
- (3) C₁₋₁₀ alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 halogens or phenyl, which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, CN, OH, R⁴, OR⁴, NH₂SO₂R⁴, SO₂R⁴, CO₂H, and CO₂C₁₋₆ alkyl, wherein the CO₂C₁₋₆ alkyl is linear or branched,
- (4) phenyl which is unsubstituted or substituted with 1-5 substituents independently selected from halogen, CN, OH, R⁴, OR⁴, NH₂SO₂R⁴,

SO_2R^4 , CO_2H , and $\text{CO}_2\text{C}_1\text{-6alkyl}$, wherein the $\text{CO}_2\text{C}_1\text{-6alkyl}$ is linear or branched, and

5 (5) a 5- or 6-membered heterocycle which may be saturated or unsaturated comprising 1-4 heteroatoms independently selected from N, S and O, the heterocycle being unsubstituted or substituted with 1-3 substituents independently selected from oxo, OH, halogen, $\text{C}_1\text{-6}$ alkyl, and $\text{C}_1\text{-6}$ alkoxy, wherein the $\text{C}_1\text{-6}$ alkyl and $\text{C}_1\text{-6}$ alkoxy are linear or branched and optionally substituted with 1-5 halogens;

10 R^4 is $\text{C}_1\text{-6}$ alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 groups independently selected from halogen, CO_2H , and $\text{CO}_2\text{C}_1\text{-6}$ alkyl, wherein the $\text{CO}_2\text{C}_1\text{-6}$ alkyl is linear or branched;

R^5 and R^6 are each independently selected from the group consisting of:

15 (1) hydrogen,
(2) $\text{C}_1\text{-10}$ alkyl, which is linear or branched and which is unsubstituted or substituted with one or more substituents selected from:
(a) halogen,
(b) hydroxy,
20 (c) phenyl, wherein the phenyl is optionally substituted with 1-5 substituents independently selected from halogen, OH, $\text{C}_1\text{-6}$ alkyl, and $\text{C}_1\text{-6}$ alkoxy, wherein the $\text{C}_1\text{-6}$ alkyl and $\text{C}_1\text{-6}$ alkoxy are linear or branched and optionally substituted with 1-5 halogens,
25 (d) naphthyl, wherein the naphthyl is optionally substituted with 1-5 substituents independently selected from halogen, OH, $\text{C}_1\text{-6}$ alkyl, and $\text{C}_1\text{-6}$ alkoxy, wherein the $\text{C}_1\text{-6}$ alkyl and $\text{C}_1\text{-6}$ alkoxy are linear or branched and optionally substituted with 1-5 halogens,
30 (e) CO_2H ,
(f) $\text{CO}_2\text{C}_1\text{-6}$ alkyl,
(g) CONR^7R^8 , wherein R^7 and R^8 are independently selected from the group consisting of hydrogen, tetrazolyl, phenyl,

C₃-6 cycloalkyl and C₁-6 alkyl, wherein C₁-6 alkyl is linear or branched and is optionally substituted with 1-6 substituents independently selected from 0-5 halogen and 0-1 phenyl, wherein the phenyl or C₃-6 cycloalkyl being R⁷ or R⁸ or the optional phenyl substituent on the C₁-6 alkyl are optionally substituted with 1-5 substituents independently selected from halogen, OH, C₁-6 alkyl, and C₁-6 alkoxy, said C₁-6 alkyl and C₁-6 alkoxy being linear or branched and optionally substituted with 1-5 halogens,

or wherein R⁷ and R⁸ are optionally joined to form a ring selected from pyrrolidine, piperidine or morpholine,

(3) CN,

(4) phenyl which is unsubstituted or substituted with 1-5 substituents independently selected from C₁-6 alkyl, C₁-6 alkoxy, hydroxy and halogen, wherein the C₁-6 alkyl and C₁-6 alkoxy are linear or branched and optionally substituted with 1-5 halogens,

(5) naphthyl which is unsubstituted or substituted with 1-5 substituents independently selected from C₁-6 alkyl, C₁-6 alkoxy, hydroxy and halogen, wherein the C₁-6 alkyl and C₁-6 alkoxy are linear or branched and optionally substituted with 1-5 halogens,

(6) CO₂H,

(7) CO₂C₁-6 alkyl,

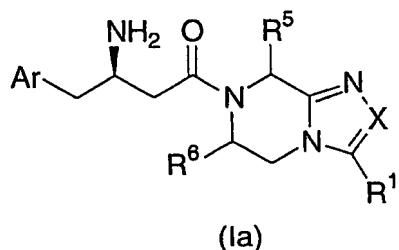
(8) CONR⁷R⁸, and

(9) C₃-6 cycloalkyl, which is optionally substituted with 1-5 substituents independently selected from halogen, OH, C₁-6 alkyl, and C₁-6 alkoxy, wherein the C₁-6 alkyl and C₁-6 alkoxy are linear or branched and optionally substituted with 1-5 halogens,

with the proviso that one of R⁵ and R⁶ is other than hydrogen; or a pharmaceutically acceptable salt thereof.

30

2. The compound of Claim 1 of the formula Ia:

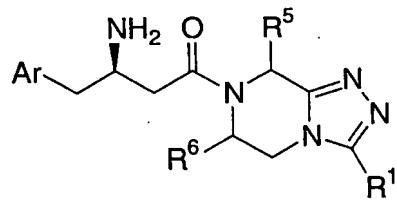


(Ia)

or a pharmaceutically acceptable salt thereof.

5

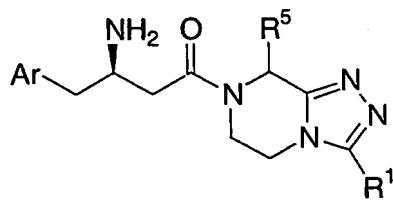
3. The compound of Claim 2 of the formula Ib:



(Ib)

or a pharmaceutically acceptable salt thereof.

4. The compound of Claim 3 of the formula Ic:

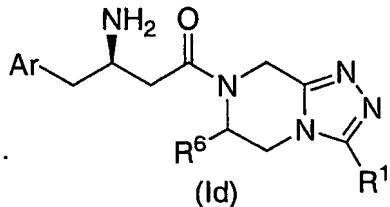


(Ic)

10

or a pharmaceutically acceptable salt thereof.

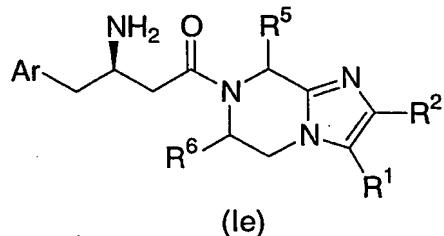
5. The compound of Claim 3 of the formula Id



or a pharmaceutically acceptable salt thereof.

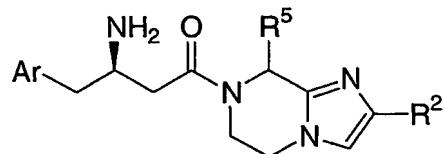
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6. The compound of Claim 2 of the formula Ie:



or a pharmaceutically acceptable salt thereof.

7. The compound of Claim 6 of the formula If:



10

(If)

or a pharmaceutically acceptable salt thereof.

8. The compound of Claim 1 wherein Ar is phenyl which is unsubstituted or substituted with 1-5 substituents which are independently selected from the group consisting of:

- (1) fluoro,
- (2) chloro, and
- (3) CF₃.

9. The compound of Claim 8 wherein Ar is selected from the group consisting of:

5 (1) phenyl,
(2) 2-fluorophenyl,
(3) 3,4-difluorophenyl,
(4) 2,5-difluorophenyl,
(5) 2,4,5-trifluorophenyl, and
(6) 2-fluoro-4-(trifluoromethyl)phenyl.

10

10. The compound of Claim 1 wherein R¹ is selected from the group consisting of:

15 (1) hydrogen and
(2) C₁₋₆ alkyl, which is linear or branched and which is unsubstituted or substituted with phenyl or 1-5 fluorines.

20

11. The compound of Claim 10 wherein R¹ is selected from the group consisting of:

(1) hydrogen,
(2) methyl,
(3) ethyl,
(4) CF₃,
(5) CH₂CF₃,
(6) CF₂CF₃, and
(7) benzyl.

25

12. The compound of Claim 11 wherein R¹ is selected from the group consisting of:

30 (1) hydrogen,
(2) methyl,
(3) ethyl,
(4) CF₃, and
(5) CH₂CF₃.

13. The compound of Claim 12 wherein R¹ is hydrogen or CF₃.

14. The compound of Claim 1 wherein R² is selected from:

5 (1) hydrogen,
(2) C₁₋₆alkyl, which is linear or branched and which is unsubstituted or substituted with 1-5 fluorines, and
(3) phenyl, which is unsubstituted or substituted with 1-3 substituents independently selected from fluoro, OCH₃, and OCF₃.

10 15. The compound of Claim 14 wherein R² is selected from the group consisting of:

(1) hydrogen,
(2) methyl,
15 (3) ethyl,
(4) CF₃,
(5) CH₂CF₃,
(6) CF₂CF₃,
(7) phenyl,
20 (8) (4-methoxy)phenyl,
(9) (4-trifluoromethoxy)phenyl,
(10) 4-fluorophenyl, and
(11) 3,4-difluorophenyl.

25 16. The compound of Claim 15 wherein R² is CF₃ or CF₂F₃.

17. The compound of Claim 1 wherein R⁵ and R⁶ are independently selected from the group consisting of:

30 (1) hydrogen,
(2) C₁₋₁₀ alkyl, which is linear or branched and which is unsubstituted or substituted with one or more substituents selected from:
(a) halogen,
(b) phenyl, wherein the phenyl is optionally substituted with 1-5 substituents independently selected from halogen, OH,

C₁-6 alkyl, and C₁-6 alkoxy, wherein the C₁-6 alkyl and C₁-6 alkoxy are linear or branched and optionally substituted with 1-5 halogens, and

5 (3) phenyl which is unsubstituted or substituted with 1-3 substituents independently selected from C₁-6alkyl, OC₁-6alkyl, and halogen, wherein the C₁-6alkyl and OC₁-6alkyl are linear or branched and optionally substituted with 1-5 halogens, and

(4) CO₂C₁-6 alkyl,
with the proviso that one of R⁵ and R⁶ is other than hydrogen.

10

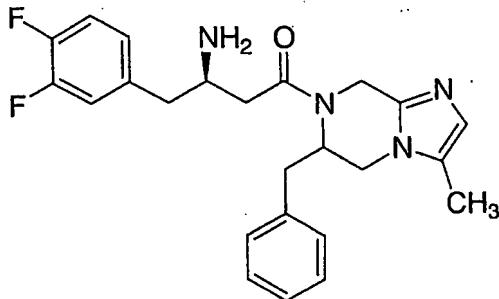
18. The compound of Claim 17 wherein R⁵ and R⁶ are independently selected from the group consisting of:

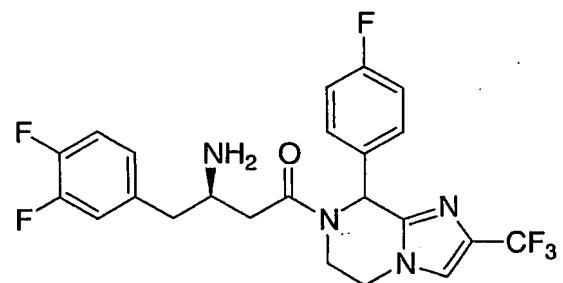
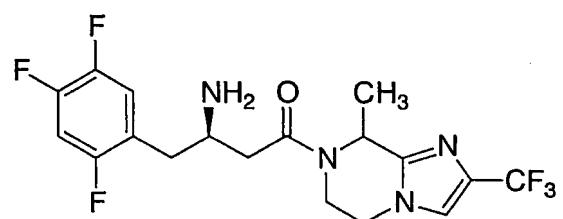
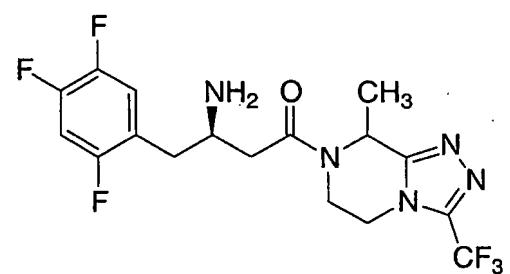
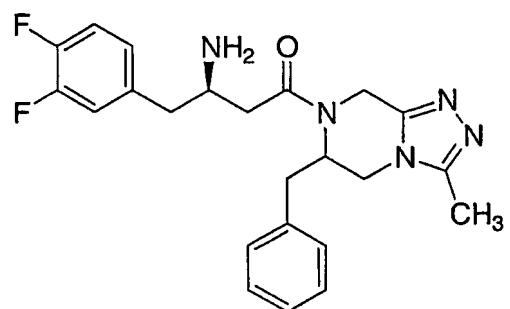
15 (1) hydrogen,
(2) CH₃,
(3) CH₂CH₃,
(4) CH(CH₃)₂,
(5) COOCH₃,
(6) CH₂-phenyl,
(7) 3-fluorophenyl, and
20 (8) 2-(trifluoromethyl)phenyl,
with the proviso that one of R⁵ and R⁶ is other than hydrogen.

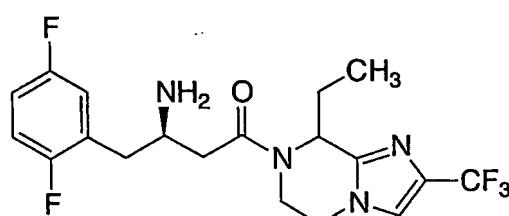
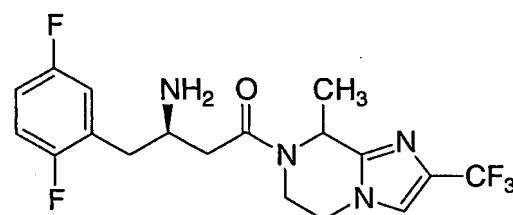
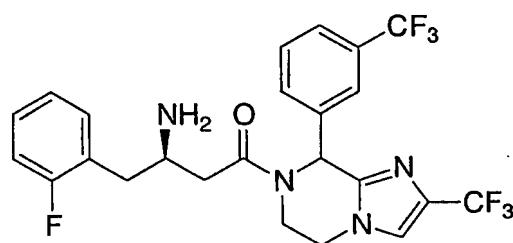
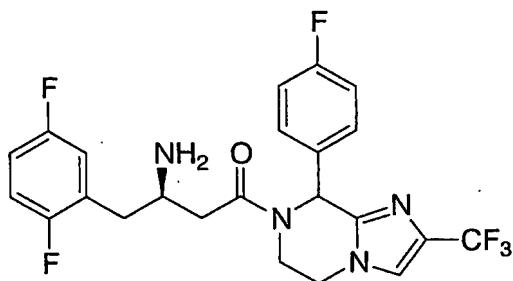
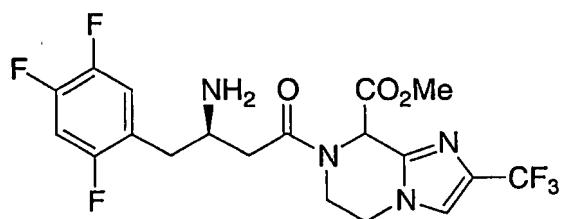
19. The compound of Claim 18 wherein R⁵ and R⁶ are independently hydrogen or CH₃, with the proviso that one of R⁵ and R⁶ is other than

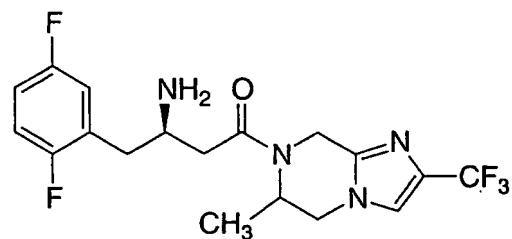
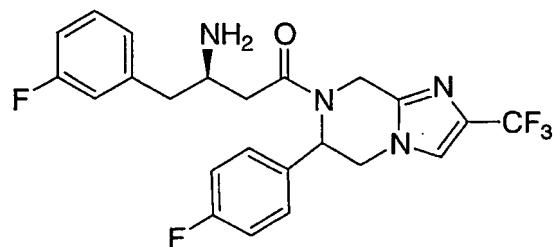
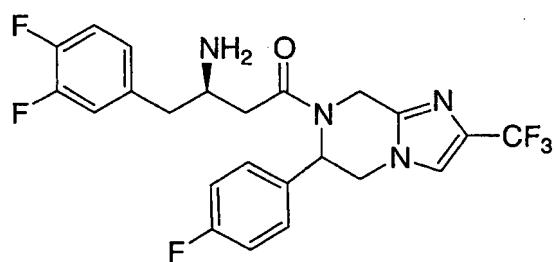
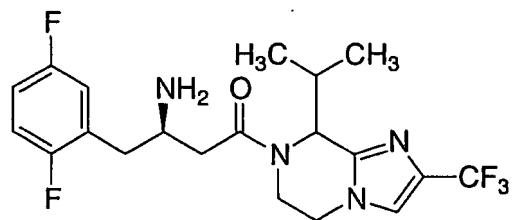
25 hydrogen.

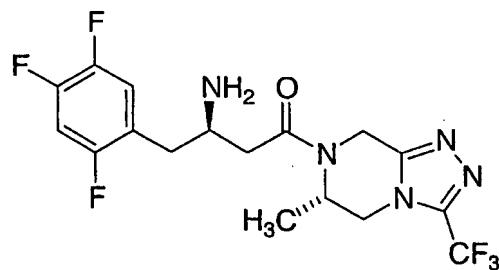
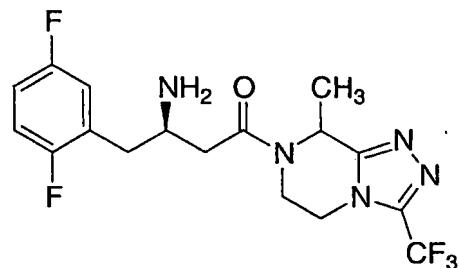
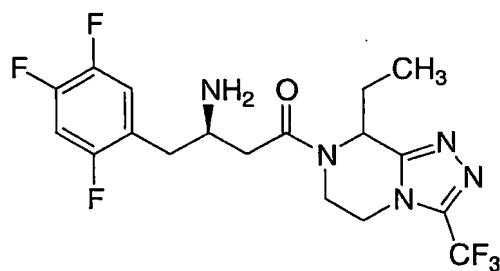
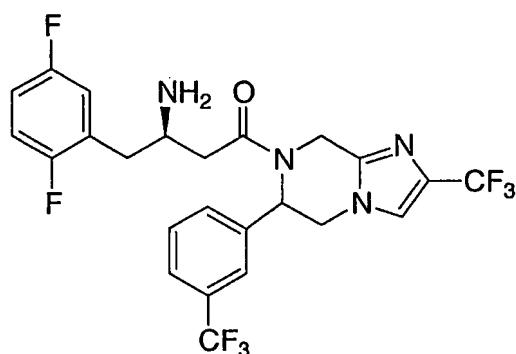
20. A compound which is selected from the group consisting of:

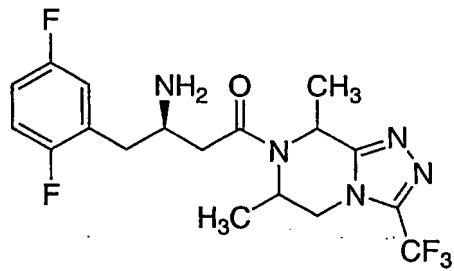
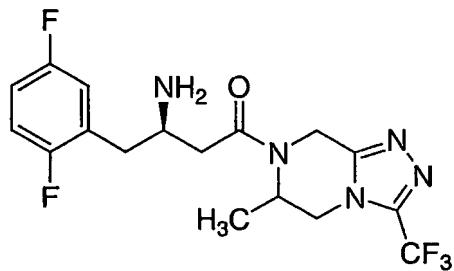
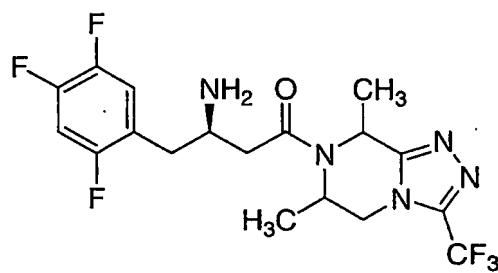
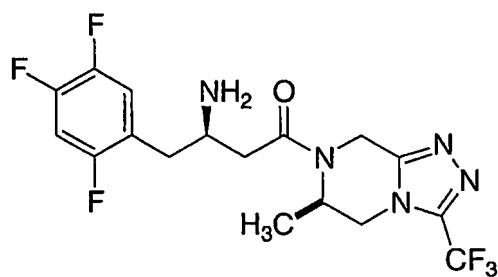












5 or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

22. A method for inhibition of dipeptidyl peptidase-IV enzyme activity in a mammal which comprises the administration to a mammalian patient in need thereof an effective amount of a compound of Claim 1.

5 23. A method for treating, controlling, ameliorating or reducing the risk of diabetes comprising the administration to a mammalian patient in need thereof a therapeutically effective amount of a compound of Claim 1.

10 24. A method for treating, controlling, ameliorating or reducing the risk of non-insulin dependent (Type 2) diabetes mellitus in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

15 25. A method for treating, controlling, ameliorating or reducing the risk of hyperglycemia in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

20 26. A method for treating, controlling, ameliorating or reducing the risk of obesity in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

25 27. A method for treating, controlling, ameliorating or reducing the risk of insulin resistance in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

30 28. A method for treating, controlling, ameliorating or reducing the risk of one or more lipid disorders selected from the group consisting of dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, and high LDL in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

29. A method for treating, controlling or preventing atherosclerosis in a mammalian patient in need of such treatment which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

5 30. A method for treating, controlling, ameliorating or reducing the risk of one or more conditions selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis 10 and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), (25) 15 hypertension and other disorders where insulin resistance is a component, in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

20 31. A method for treating, controlling, ameliorating or reducing the risk of one or more conditions selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) irritable bowel syndrome, (15) inflammatory bowel disease, including Crohn's disease and ulcerative colitis, (16) other inflammatory conditions, (17) pancreatitis, (18) abdominal obesity, (19) neurodegenerative disease, (20) retinopathy, (21) nephropathy, (22) neuropathy, (23) Syndrome X, (24) ovarian hyperandrogenism (polycystic ovarian syndrome), (25) Type 2 diabetes, (26) growth hormone deficiency, (27) neutropenia, (28) neuronal 25 disorders, (29) tumor metastasis, (30) benign prostatic hypertrophy, (32) gingivitis, (33) hypertension, (34) osteoporosis, and other conditions that may be affected by inhibition of DP-IV, in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of a first compound of Claim 1, or a pharmaceutically acceptable salt thereof, and one or more other 30 compounds selected from the group consisting of:

- (a) other dipeptidyl peptidase IV (DP-IV) inhibitors;
- (b) insulin sensitizers selected from the group consisting of (i) PPAR γ agonists, other PPAR ligands, PPAR α/γ dual agonists, and PPAR α agonists, (ii) biguanides, and (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;
- 5 (c) insulin or insulin mimetics;
- (d) sulfonylureas or other insulin secretagogues;
- (e) α -glucosidase inhibitors;
- (f) glucagon receptor agonists;
- (g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists;
- 10 (h) GIP, GIP mimetics, and GIP receptor agonists;
- (i) PACAP, PACAP mimetics, and PACAP receptor agonists;
- (j) cholesterol lowering agents selected from the group consisting of (i) HMG-CoA reductase inhibitors, (ii) sequestrants, (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonists, (v) PPAR α/γ dual agonists, (vi) inhibitors of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitors, and (viii) anti-oxidants;
- 15 (k) PPAR δ agonists;
- (l) antiobesity compounds;
- (m) ileal bile acid transporter inhibitors;
- 20 (n) antihypertensives; and
- (o) anti-inflammatory agents.

32. A method for treating, controlling, ameliorating or reducing the risk of one or more conditions selected from the group consisting of 25 hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia, and dyslipidemia, which method comprises administering to a mammalian patient in need thereof a therapeutically effective amount of a compound of Claim 1 and an HMG-CoA reductase inhibitor.

30 33. The method of Claim 32 wherein the HMG-CoA reductase inhibitor is a statin.

34. The method of Claim 33 wherein the statin is selected from the 35 group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, and rosuvastatin.

35. A method for treating, controlling, ameliorating or reducing the risk of atherosclerosis in a mammalian patient in need thereof comprising the administration to the patient of an effective amount of a compound of Claim 1 and an 5 effective amount of an HMG-CoA reductase inhibitor.

36. The method of Claim 35 wherein the HMG-CoA reductase inhibitor is a statin.

10 37. The method of Claim 36 wherein the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, and rosuvastatin.

15 38. A pharmaceutical composition for treating, controlling, ameliorating or reducing the risk of atherosclerosis, comprising: (1) a compound of Claim 1, (2) an HMG-CoA reductase inhibitor, and (3) a pharmaceutically acceptable carrier.

20 39. A method of treating diabetes in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1 in combination with the PPAR α/γ dual agonist KRP-297.

25 40. The pharmaceutical composition of Claim 21 further comprising one or more additional active ingredients selected from the group consisting of:

- (a) a second dipeptidyl peptidase IV inhibitor;
- (b) an insulin sensitizer selected from the group consisting of a PPAR γ agonist, a PPAR α/γ dual agonist, a PPAR α agonist, a biguanide, and a protein tyrosine phosphatase-1B inhibitor;
- (c) an insulin or insulin mimetic;
- (d) a sulfonylurea or other insulin secretagogue;
- (e) an α -glucosidase inhibitor;
- (f) a glucagon receptor antagonist;
- (g) GLP-1, a GLP-1 mimetic, or a GLP-1 receptor agonist;
- (h) GIP, a GIP mimetic, or a GIP receptor agonist;

- (i) PACAP, a PACAP mimetic, or a PACAP receptor agonist;
- (j) a cholesterol lowering agent such as (i) HMG-CoA reductase inhibitor, (ii) sequestrant, (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPAR α agonist, (v) PPAR α/γ dual agonist, (vi) inhibitor of cholesterol absorption, 5 (vii) acyl CoA:cholesterol acyltransferase inhibitor, and (viii) anti-oxidant;
- (k) a PPAR δ agonist;
- (l) an antiobesity compound;
- (m) an ileal bile acid transporter inhibitor;
- (n) an anti-inflammatory agent; and
- 10 (o) an antihypertensive agent.

41. The pharmaceutical composition of Claim 40 wherein the PPAR α/γ dual agonist is KRP-297.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 October 2003 (09.10.2003)

PCT

(10) International Publication Number
WO 03/082817 A3

(51) International Patent Classification⁷: C07D 211/36, (74) Common Representative: MERCK & CO., INC.; 126 A61K 31/495 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(21) International Application Number: PCT/US03/08723

(22) International Filing Date: 21 March 2003 (21.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/367,410 25 March 2002 (25.03.2002) US

(71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

(88) Date of publication of the international search report: 18 December 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



WO 03/082817 A3

(54) Title: BETA-AMINO HETEROCYCLIC DIPEPTIDYL PEPTIDASE INHIBITORS FOR THE TREATMENT OR PREVENTION OF DIABETES

(57) Abstract: The present invention is directed to compounds which are inhibitors of the dipeptidyl peptidase-IV enzyme ("DP-IV inhibitors") and which are useful in the treatment or prevention of diseases in which the dipeptidyl peptidase-IV enzyme is involved, such as diabetes and particularly type 2 diabetes. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which the dipeptidyl peptidase-IV enzyme is involved.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/08723

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 211/36; A61K 31/495
US CL. : 546/236; 514/254 DS

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/236; 514/254.05

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST: STN CAS ON LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,939,560 A (JENKINS et al) 17 August 1999 (17.08.1999), entire document	1-41
A	US 5,200,412 A (WHITTAKER et al) 06 April 1993 (06.04.1993), entire document	1-41

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Date of the actual completion of the international search

Date of mailing of the international search report:

07 August 2003 (07.08.2003)

09 SEP 2003

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